

Swiss TPH Hybrid Symposium: The Tuberculosis Pandemic – a Call to Action
22 March 2023

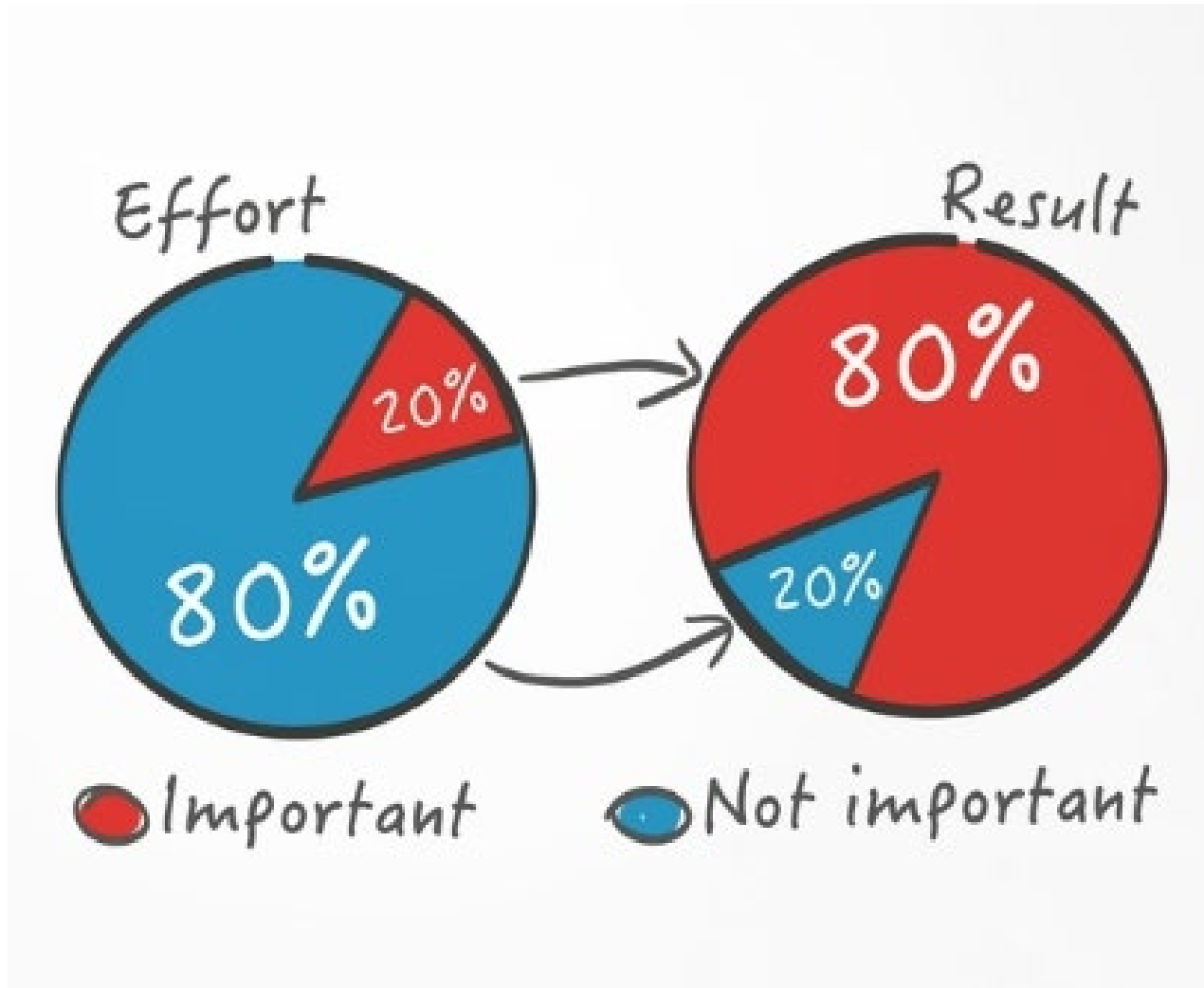
Paediatric TB: Doing More with Less

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- **Head Mycobacterial and Migrant Health Research**
University Children's Hospital Basel
Department for Clinical Research University of Basel

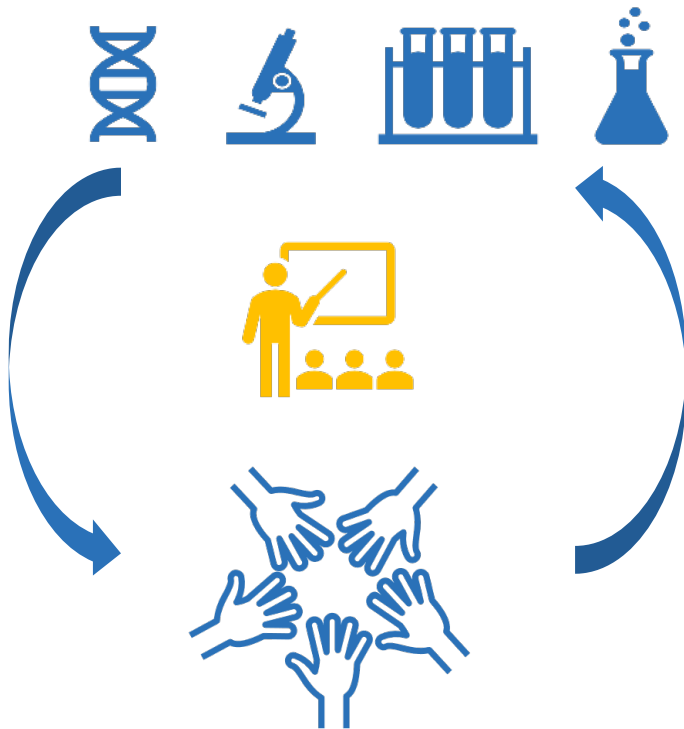


Doing more with less



From Science to Impact

*“good care comes with
and from good science”*



Clinical care: A case

14 y old adolescent

3 months of recurrent lower
respiratory tract infections
weight loss, fatigue
cannot join soccer training
any more

Arrived in Switzerland 5
years earlier, from Pakistan



Clinical care: Index case? TB exposed?

- Mother, father
sister, 3 y old
brother, 10 y old



- School



- Soccer club

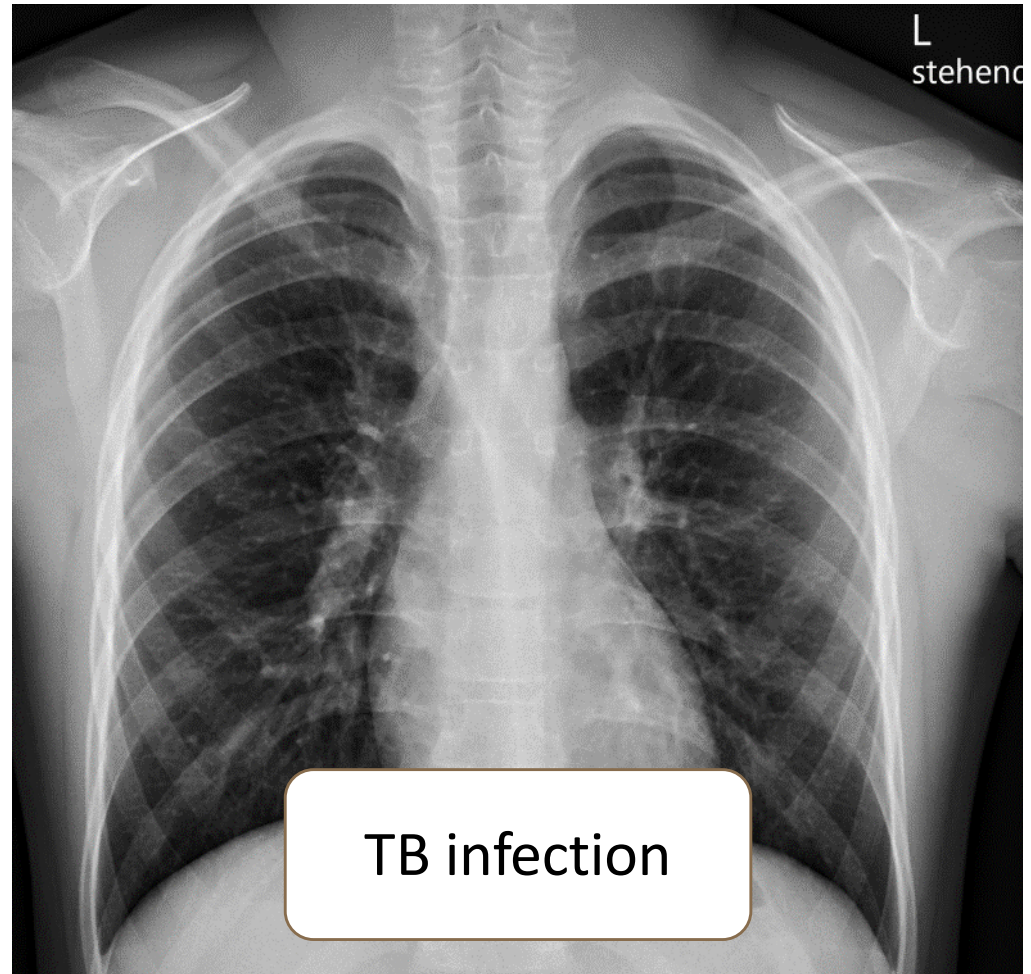


10 y old brother

No clinical symptoms

IGRA positive

Chest x-ray



TB infection

3 y old sister

Currently health but...

2-3 respiratory infections
in the last few months

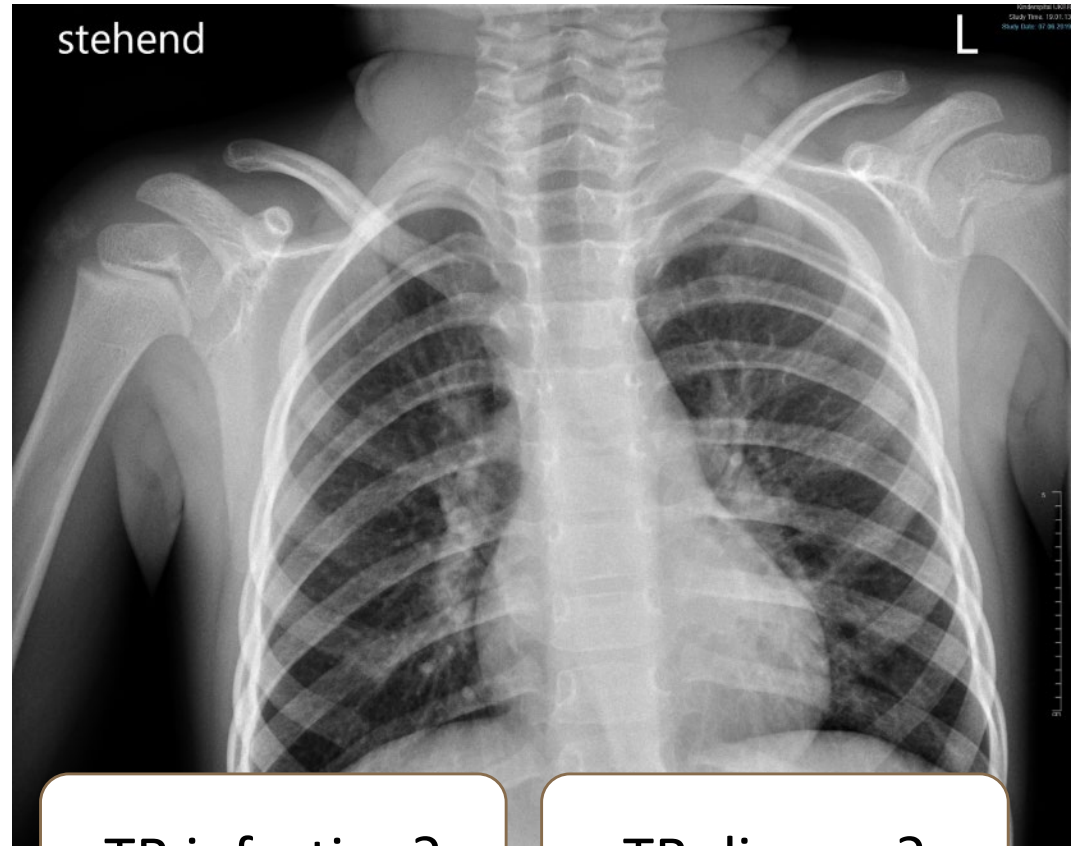
TST and IGRA positive

Chest x-ray

Admission to hospital

Induced sputum and

Gastric aspirates



TB infection?

TB disease?

Challenges and gaps in detection of childhood TB

“Our biggest challenge is collecting a sputum sample from the child to test for TB. While sputum is the standard specimen that we use to detect TB, small children are often not able to produce sufficient sputum to test.”

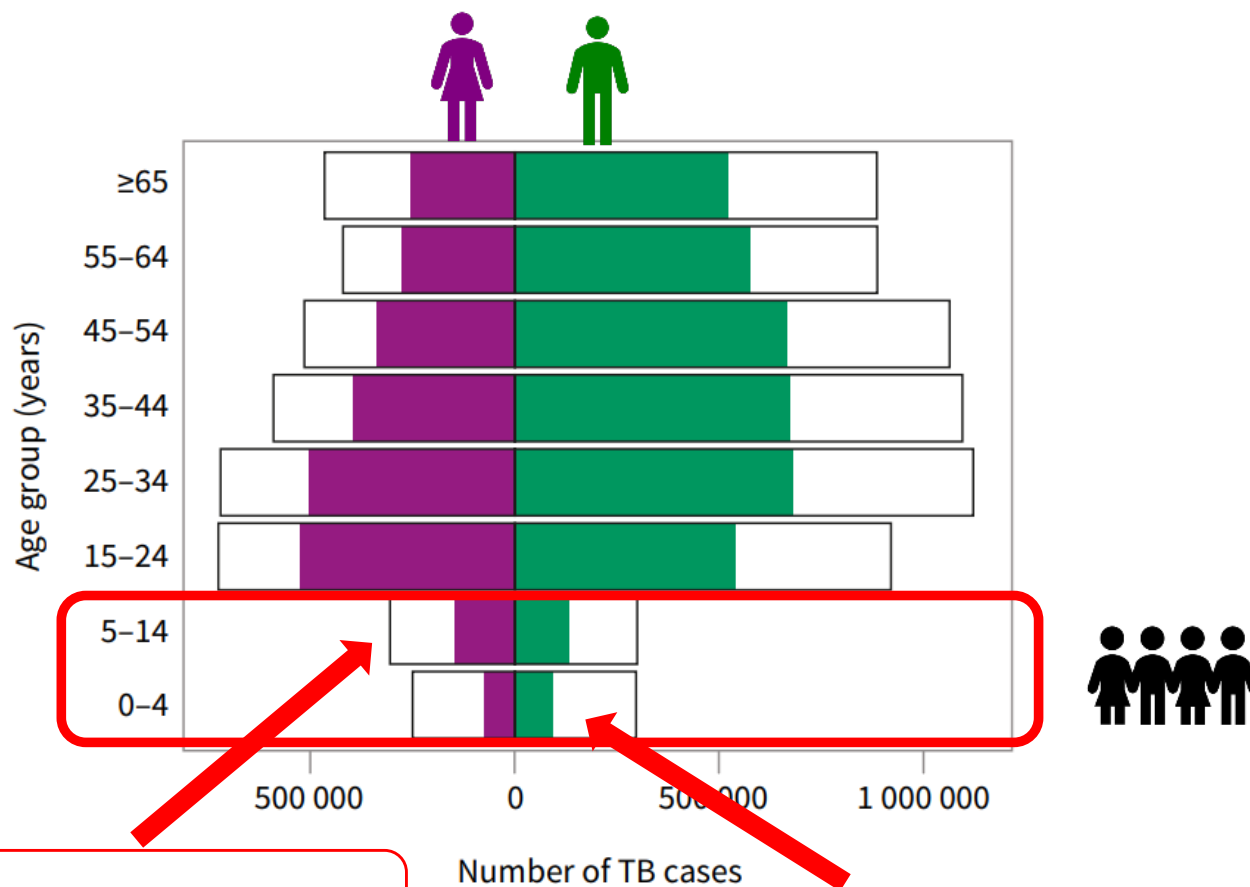
- Dr Lazro Fidelle, Malakal, South Sudan

“In our clinic, every day we see children with symptoms that could be TB. We are an experienced team and have the laboratory TB tests available but for most children who come to us, we just cannot confirm the diagnosis of TB.”

- Dr Lazro Fidelle, Malakal, South Sudan



Challenges and gaps in detection of childhood TB

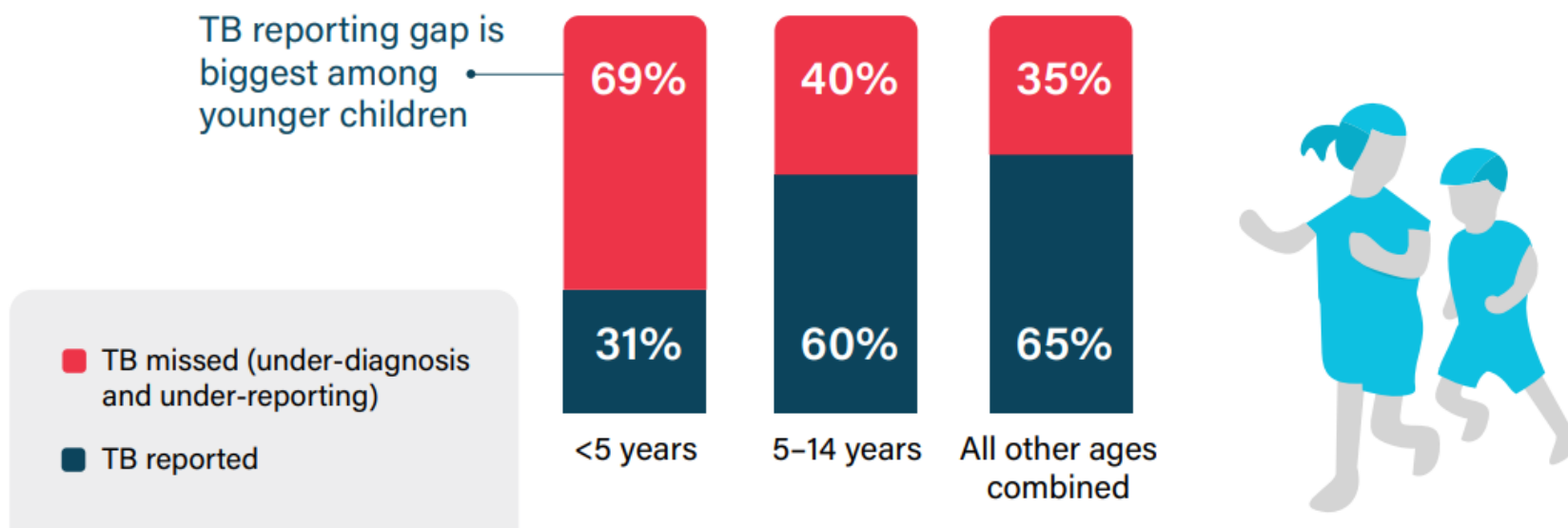


50-60% detection gap

70-80% detection gap

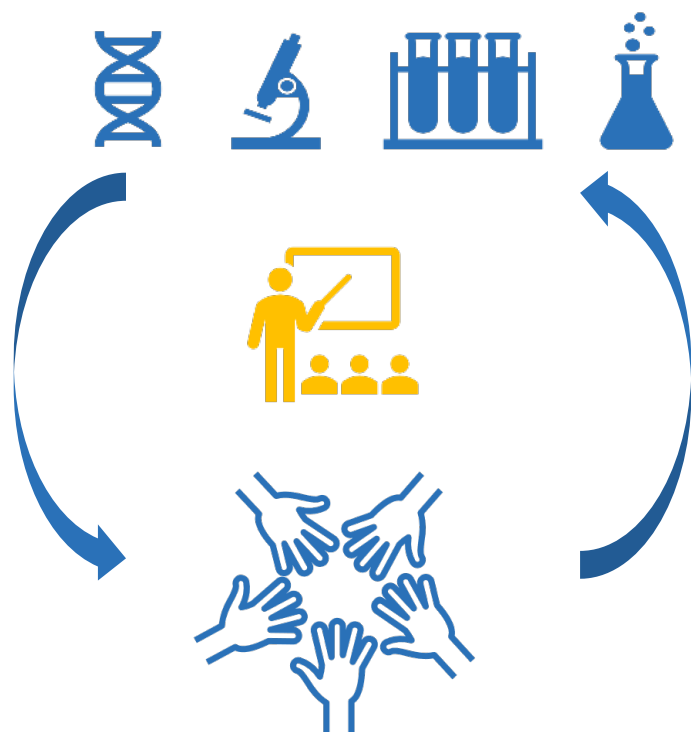
Challenges and gaps in detection of childhood TB

% of TB patients that are missed in different age groups



From Science to Impact: Main gaps in detection and treatment

*“good care comes with
and from good science”*

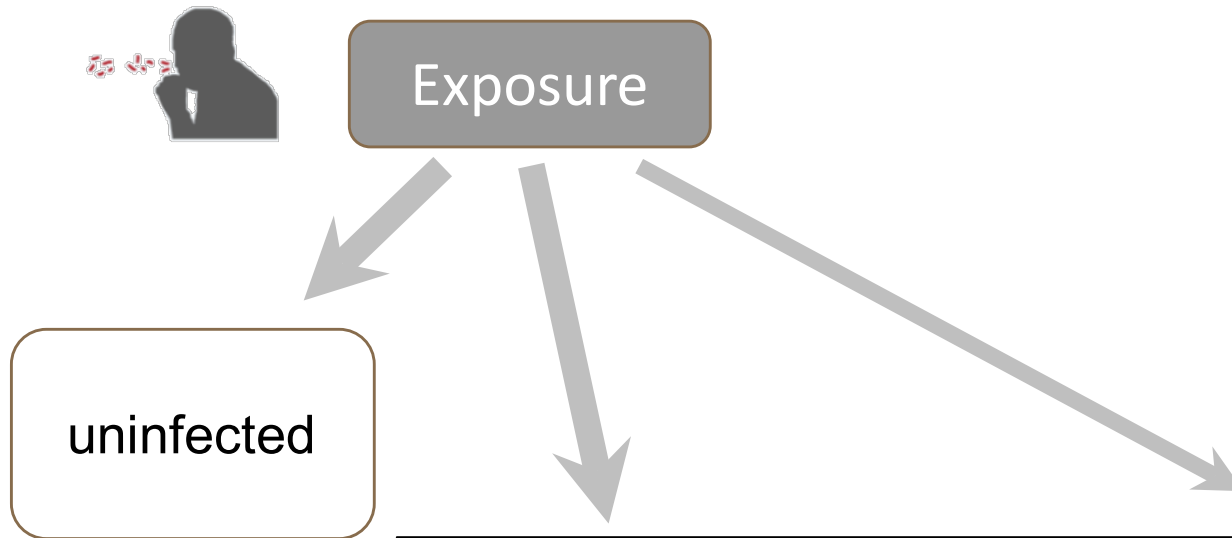


Clinical presentation

Child-friendly testing

Short and easy to
administer treatment

LTBI and active TB: the classical thinking



Brief Reviews

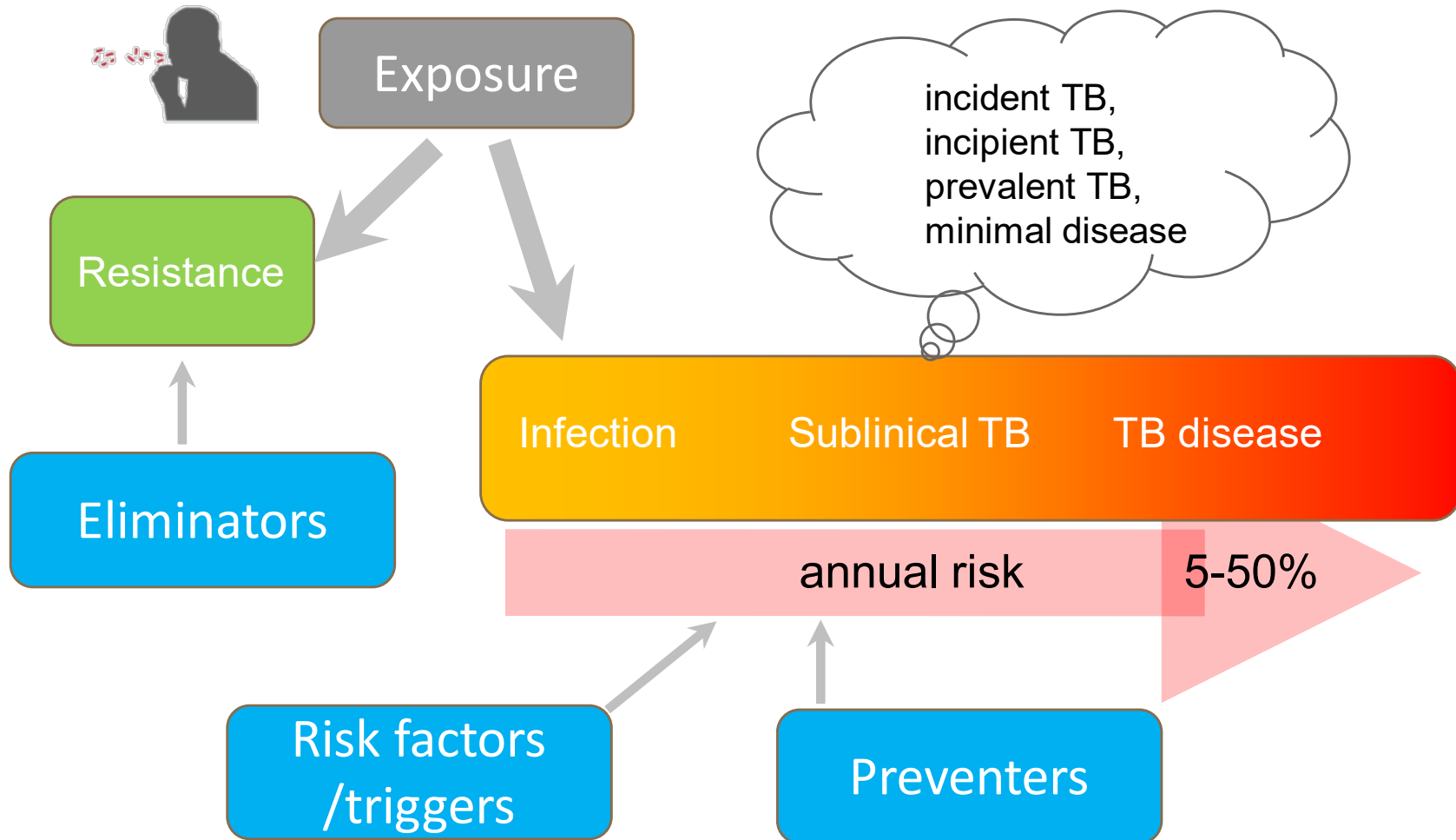
The Journal
of Immunology

The End of the Binary Era: Revisiting the Spectrum of Tuberculosis

Philana Ling Lin* and JoAnne L. Flynn[†]

[J Immunol.](#) 2018 Nov 1;201(9):2541-2548. doi: 10.4049/jimmunol.1800993.

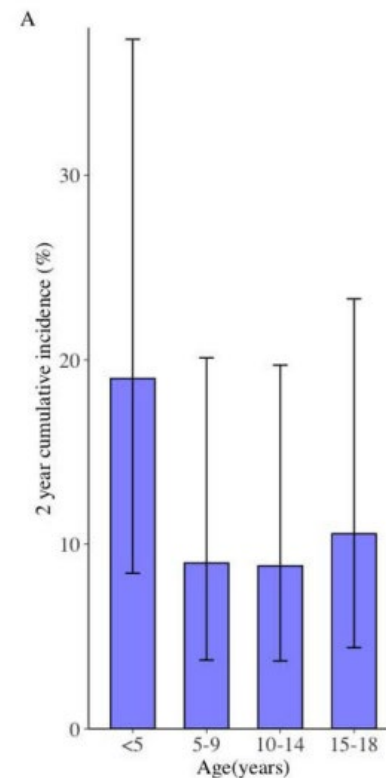
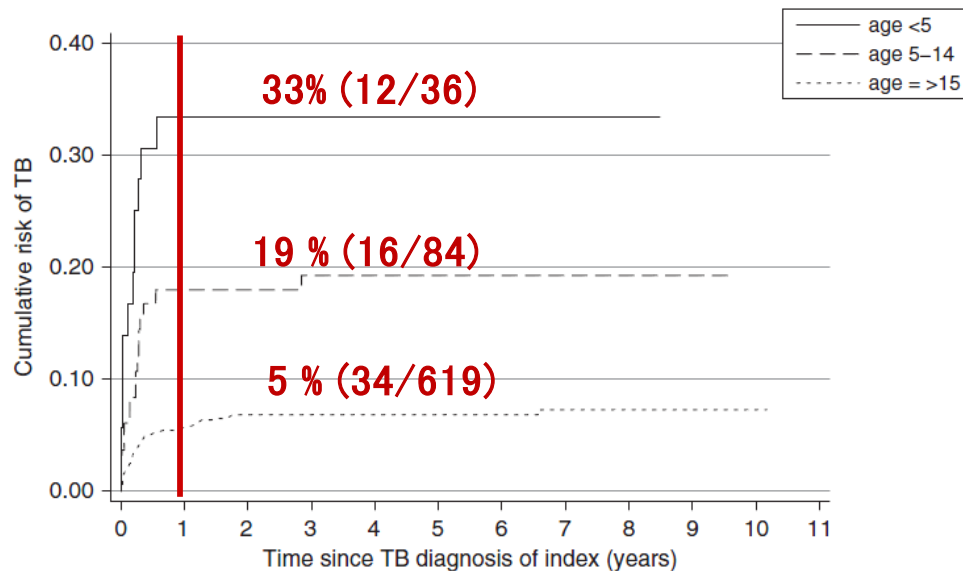
TB infection and disease a continuum



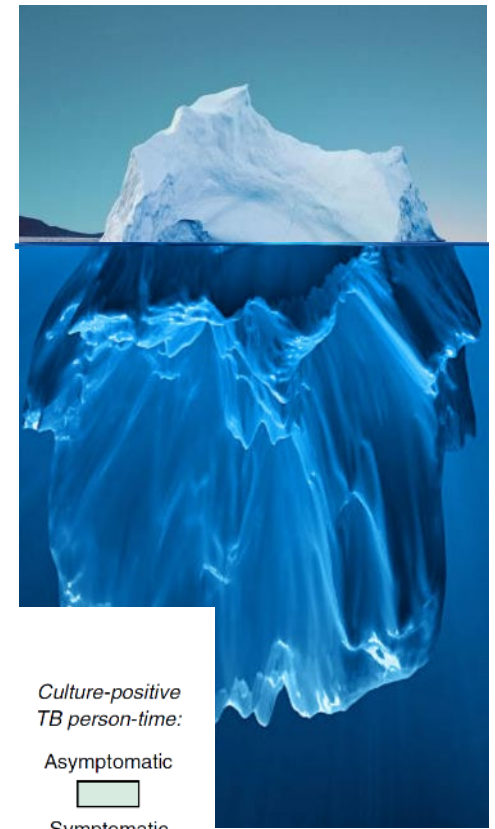
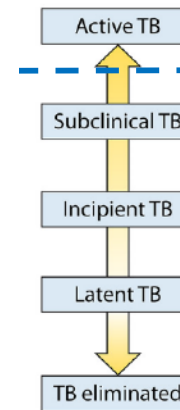
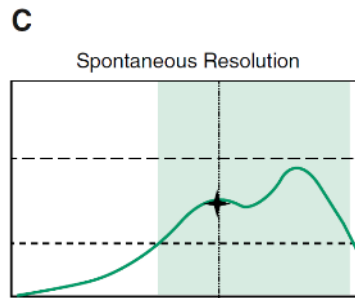
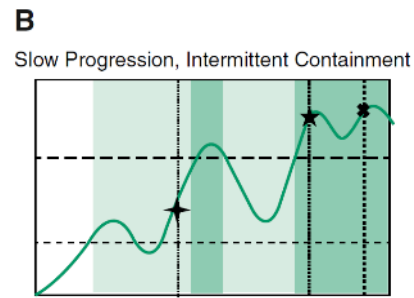
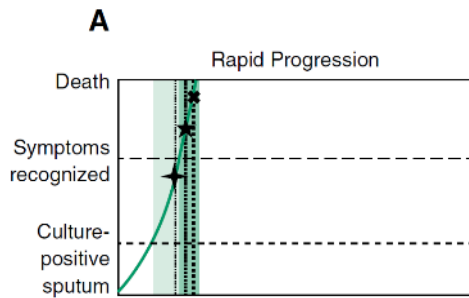
Risk of progression in children

Amsterdam (2001-2011)
610 index patients with TB
9332 contacts, 1519 (16%) < 15 years
739 (16%) had TB infection
71 (9.6% developed) TB disease

Meta-analysis 46 studies:
137,647 exposed children
followed for 429,538 child-years



What lies below the surface

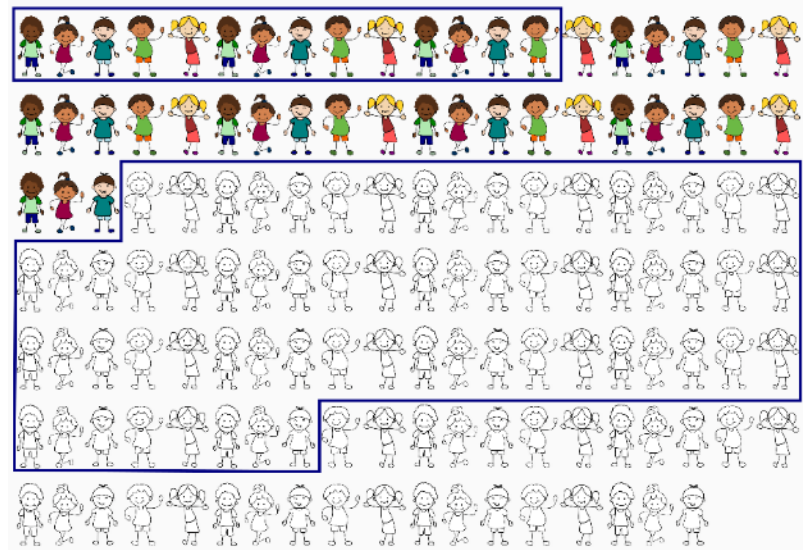


Culture-positive TB person-time:
 Asymptomatic
 Symptomatic

Can TB be asymptomatic?

- Swiss Pediatric Surveillance Unit (SPSU)
- Age < 16 years, Dec 2013 - Nov 2019

- N = 138 children
- Subclinical TB: 43 (31%)
- Culture or molecular confirmation:
 - overall 80 (58%)
 - subclinical 15 (35%)
 - symptomatic 65 (69%)



Subclinical TB is important in younger children

2022 SWISS TB AWARD



	Subclinical (N = 43)	Symptomatic (N = 95)	Total (N = 138)	P Value ^a
Age, y Median (IQR)	3.7 (2.2, 9.7)	9.7 (2.7, 14.5)	7.1 (2.7, 13.8)	.003
Gender male	21 (48.8%)	55 (57.9%)	76 (55.1%)	.322
Confirmed by culture or molecular assay	15 (34.9%)	65 (69.1%)	80 (58.4%)	<.001
Confirmed by culture	13 (30.2%)	60 (63.8%)	73 (53.3%)	<.001
Confirmed by molecular assay	5 (11.6%)	44 (46.3%)	49 (35.5%)	<.001
Confirmed by culture and molecular assay	3 (7.0%)	39 (41.1%)	42 (30.4%)	<.001
Abnormal chest radiography	41 (95.3%)	83 (89.2%)	124 (91.2%)	.243
Index case known	39 (90.7%)	49 (51.6%)	88 (63.8%)	<.001
TST positive	19 (67.9%)	38 (84.4%)	57 (78.1%)	.096
IGRA positive	20 (76.9%)	53 (89.8%)	73 (85.9%)	.115
Origin foreign-born	12 (29.3%)	52 (55.3%)	64 (47.4%)	.005

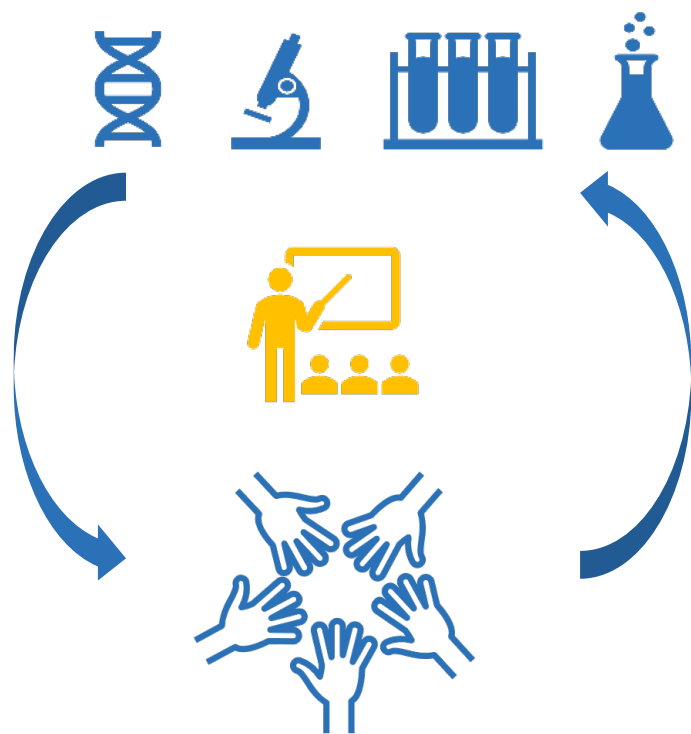
Abbreviations: IGRA, interferon gamma release assay; IQR, interquartile range; TB, tuberculosis; TST, tuberculin skin test.

^aP-value compares children with subclinical and symptomatic TB disease.

Symptoms not reported
Symptoms not notabel

From Science to Impact

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and from good science”*

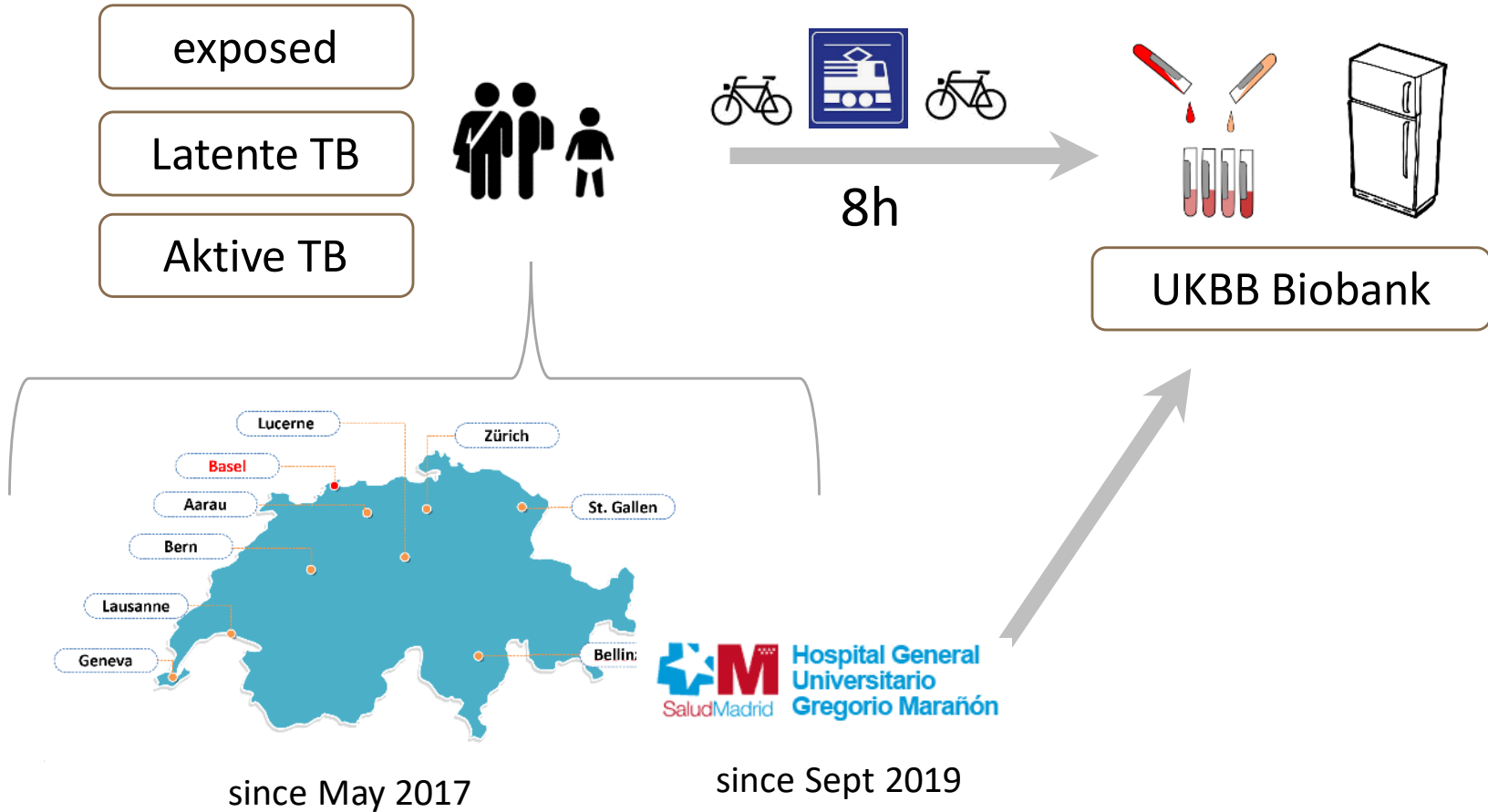


Clinical presentation

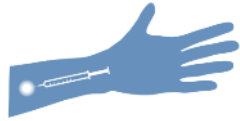
Child-friendly testing

Short and easy to
administer treatment

TubeRcUloSis infection and disease in Switzerland: CITRUS study



Immunodiagnostic tests

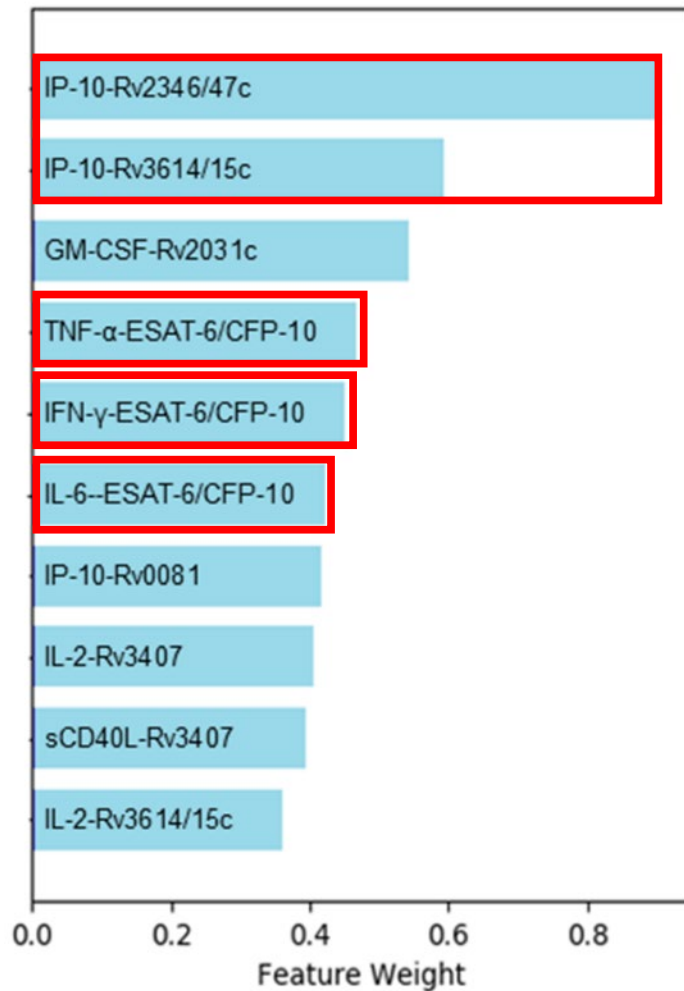


	Tuberkulin Skin Test	TB blood test (IGRA)
Synonym	Mantoux	IGRA, QuantiFERON, T-Spot. <i>TB</i>
Introduction	1907	2001
Antigen	PPD purified protein derivative	Specific TB-antigen ESAT-6/CFP-10
Measures	Skin induration (memory CD4 T-cells)	IFN-gamma
Sensitivity for TB disease	60-80%	60-80%
Disadvantages	False positive in BCG immunised Correct application and reading	Lower sensitivity in younger children Skilled lab and High cost

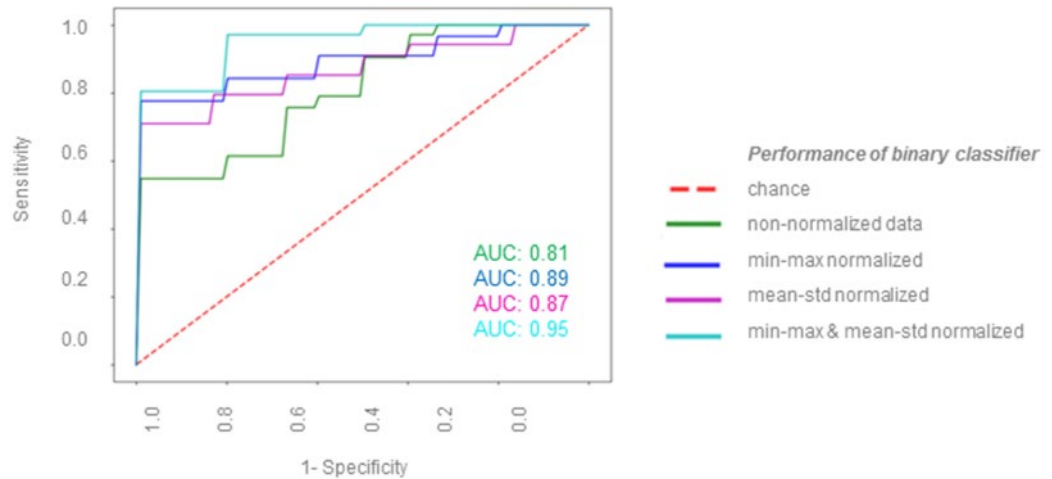
No stage specific diagnosis (infection, risk of progression, disease)

A negative test cannot be used to exclude TB

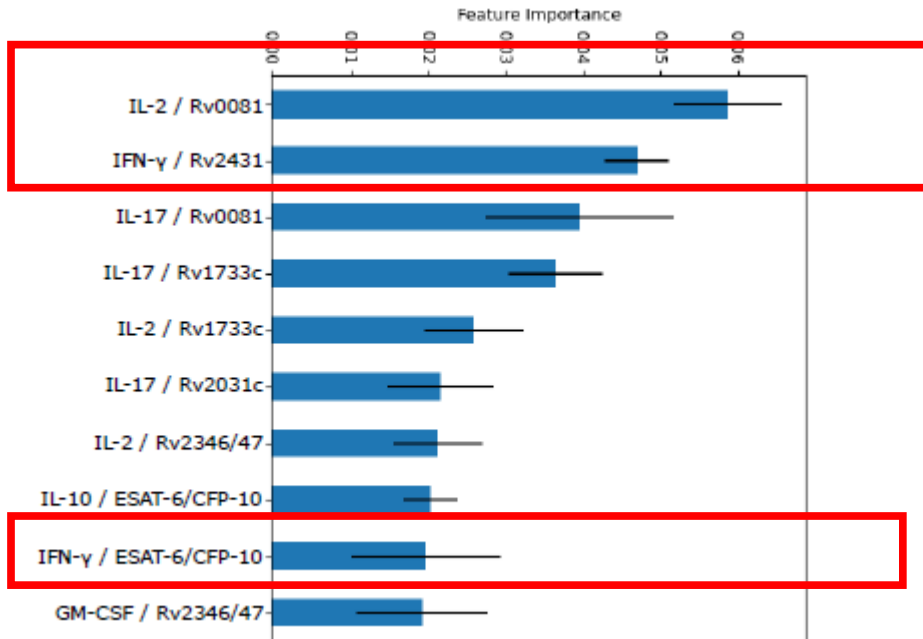
Improving IGRA sensitivity is possible



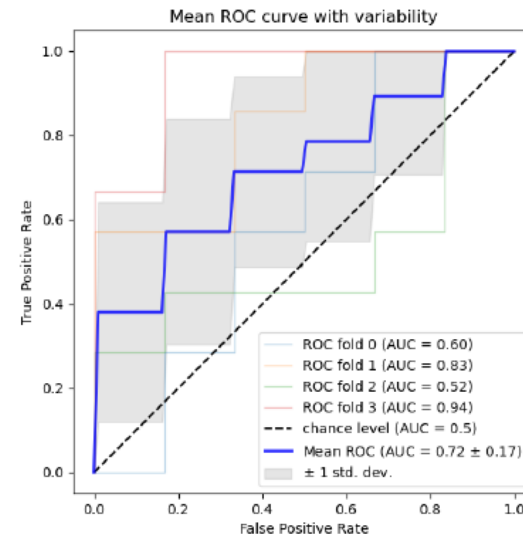
59 children
(pilot study)



Stage specific diagnosis: not yet there....



107 children
24 aTB
28 LTBI
55 exposed non
infected



Ratios: Monocyte/Lymphocyte (MLR)

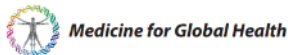
Ratio of Monocytes to Lymphocytes in Peripheral Blood Identifies Adults at Risk of Incident Tuberculosis Among HIV-Infected Adults Initiating Antiretroviral Therapy

Vivek Naranbhai,^{1,3} Adrian V. S. Hill,^{1,2} Salim S. Abdool Karim,³ Kogieleum Naidoo,³ Quarraisha Abdool Karim,³ George M. Warimwe,² Helen McShane,² and Helen Fletcher²

¹Wellcome Trust Centre for Human Genetics and ²The Jenner Institute, Nuffield Department of Medicine, University of Oxford, United Kingdom;

³Center for the AIDS Program of Research in South Africa, University of KwaZulu Natal, Durban

Naranbhai et al. *BMC Medicine* 2014, **12**:120
<http://www.biomedcentral.com/1741-7015/12/120>

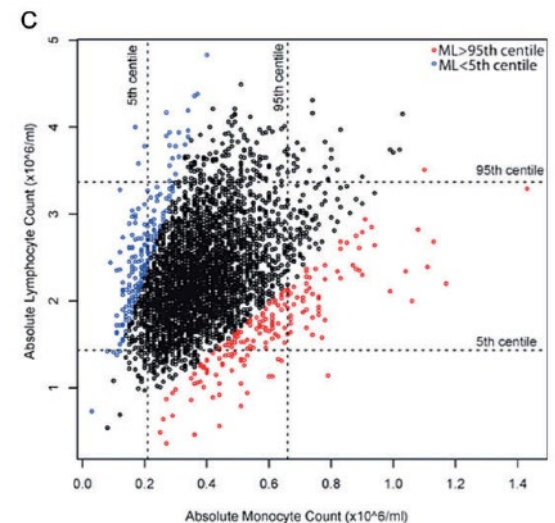


RESEARCH ARTICLE

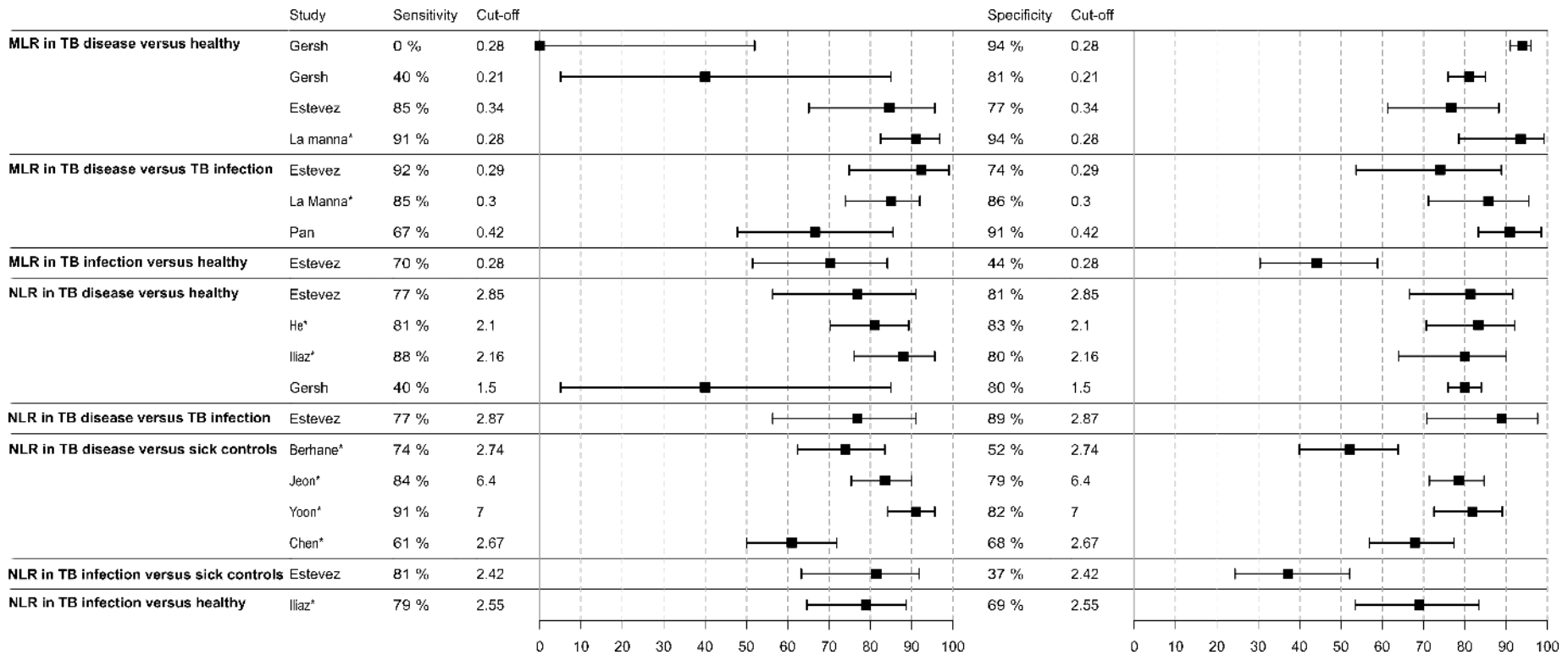
Open Access

The association between the ratio of monocytes: lymphocytes at age 3 months and risk of tuberculosis (TB) in the first two years of life

Vivek Naranbhai^{1,2}, Soyeon Kim³, Helen Fletcher⁴, Mark F Cotton⁵, Avy Violari⁶, Charles Mitchell⁷, Sharon Nachman⁸, George McSherry⁹, Helen McShane⁴, Adrian VS Hill^{1,4*}, Shabir A Madhi^{10*} for the IMPAACT P1041 team



Systematic review on full blood count ratios




Swiss data from the CITRUS cohort and the proPaed cohort

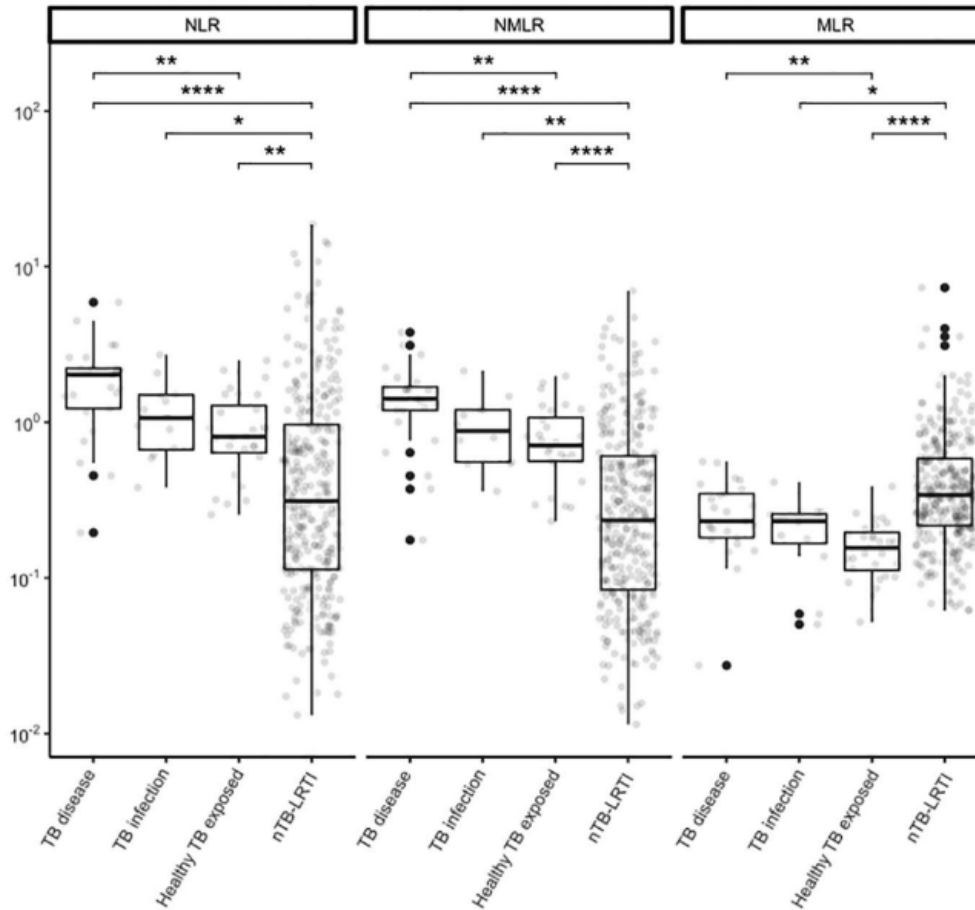
exposed

latent TB

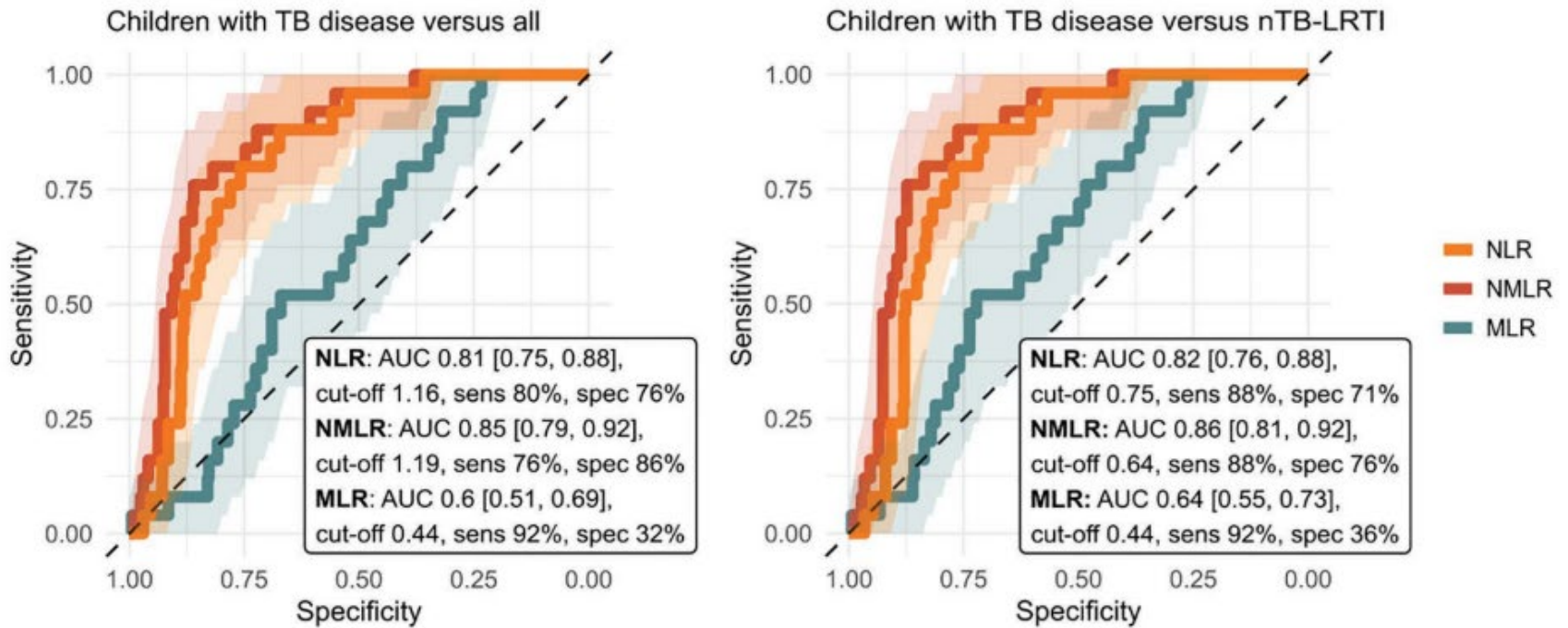
Active TB




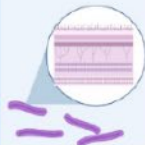







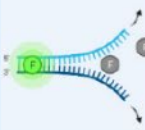



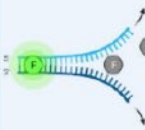







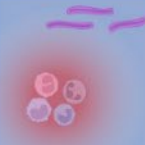


Sick controls



Swiss data from the CITRUS cohort and the proPaed cohort

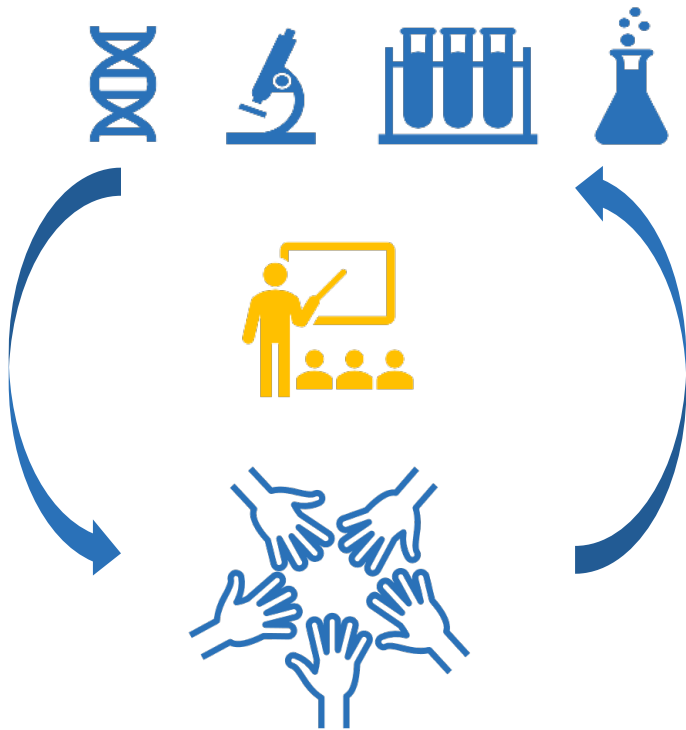


Existing and ideal point of care tests for TB

	POCT	Target	Implementation	Advantages	Disadvantages	Sensitivity	Specificity	Child-friendly	User-friendly
LAM			- Rule-in test for inpatient setting in HIV-pos. or ill individuals	- Non-invasive - Laboratory independent	- Low sensitivity in HIV-neg. patients	42-65%	84-95%		
LAMP			- Settings without access to GeneXpert instruments	- 1-h turnaround - Minimal training - Visual result interpretation	- No detection of drug-resistance - Validated on sputum only	78%	98%		
Xpert Omni*			- Remote, low-throughput settings with limited infrastructure	- Detection of drug-resistance - Mobile-phone operated	- Sputum-based test	n.d.	n.d.		
TrueNat			- Health care centers in remote areas	- Detection of drug-resistance - Battery operated - Minimal training	- Low sensitivity in smear-negative, culture-positive individuals - Sputum-based test	n.d.	n.d.		
POCUS			- Low-ressource setting with limited diagnostic infrastructure	- Non-invasive - Beneficial in treatment monitoring	- Uncertain sensitivity and specificity - Limited data on chest-POCUS in children	n.d.	n.d.		
"ideal" TB-POCT			- Rule-in test for in- and outpatient setting including remote areas	- Cheap - Fast - Detection of drug-resistance	-	≥ 66%	≥ 98%		

From Science to Impact

*“good care comes with
and from good science”*



Clinical presentation

Child-friendly testing

Short and easy to
administer treatment

The “big four” for TB treatment

Medicine	Dosage (mg/kg)^a
Isoniazid (H)	10 (range 7–15)
Rifampicin (R)	15 (range 10–20)
Pyrazinamide (Z)	35 (range 30–40)
Ethambutol (E)	20 (range 15–25)

^aAs children approach a body weight of 25 kg, adult dosages can be used.



Shorter treatment duration

The NEW ENGLAND JOURNAL of MEDICINE

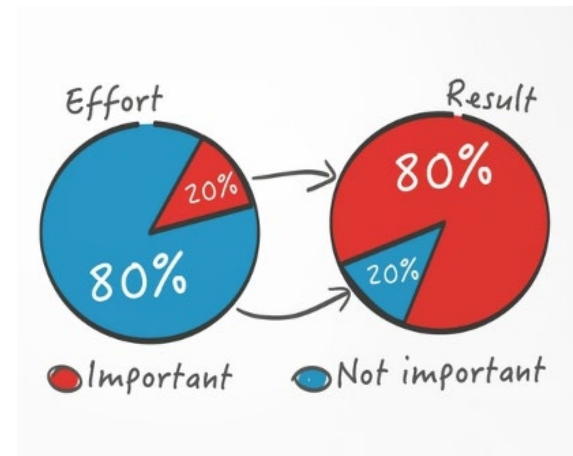
ESTABLISHED IN 1812

MARCH 10, 2022

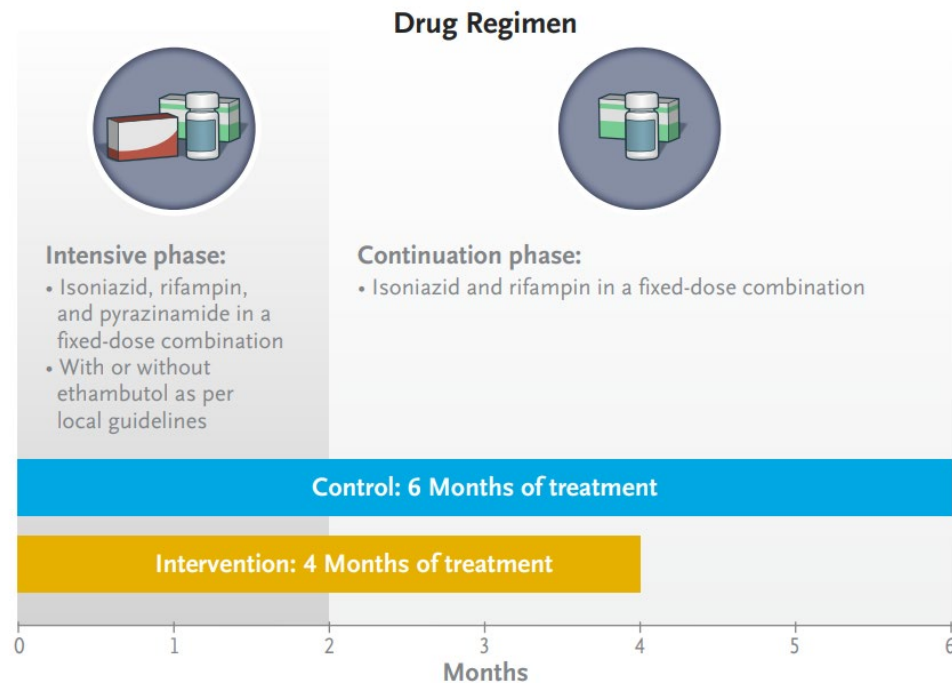
VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesselning, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*



Shine trial design



Inclusion criteria

3 months to 16 years

No “severe” TB

TB confined to one lobe (opacification of <1 lobe)

No cavities

No signs of miliary TB

No complex pleural effusion, and no clinically significant

No airway obstruction

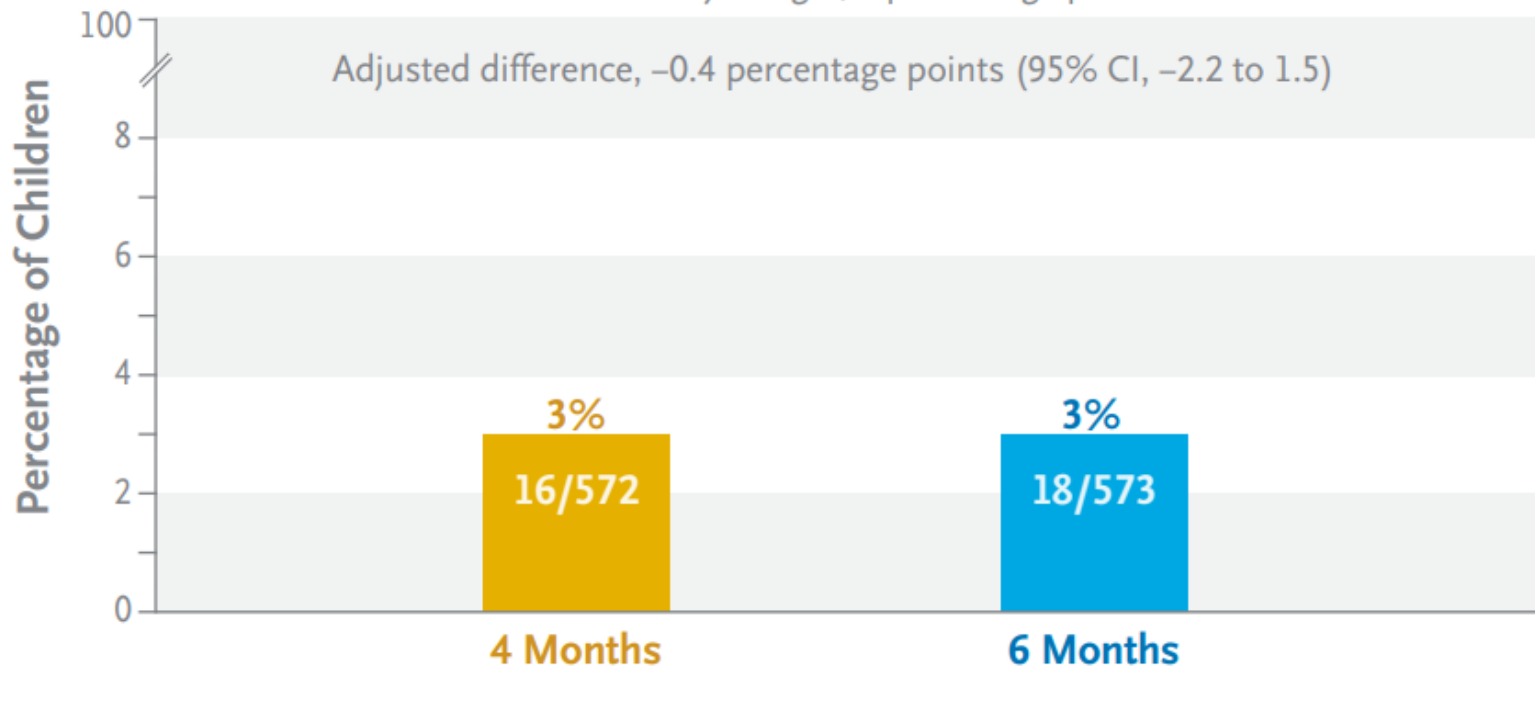
Smear negative

Drug susceptible TB

Shine results

Unfavorable Status by 72 Weeks

Excluding Children Who Did Not Complete 4 Months of Treatment
Noninferiority margin, 6 percentage points

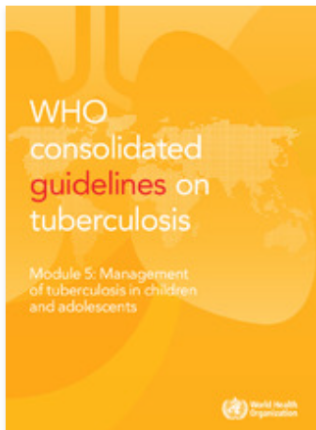


Changes in WHO guidelines

WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents

management of tuberculosis in children and adolescents

21 September 2022 | Guideline



Overview

The Updated guidelines on *Management of tuberculosis in children and adolescents* include new recommendations that cover diagnostic approaches for TB, shorter treatment for children with non-severe drug-susceptible TB, a new option for the treatment of TB meningitis, the use of bedaquiline and delamanid in young children with multidrug- and rifampicin-resistant TB and decentralized and family-centred, integrated models of care for TB case detection and prevention in children and adolescents.

The desired impact of WHO normative guidance on the management of TB in children and adolescents is a reduction in the burden of TB morbidity and mortality in children and adolescents, in line with the targets included in the WHO End TB Strategy, goal 3 of the United Nations Sustainable Development Goals and the Political Declaration of the United Nations General Assembly High-level Meeting on the Fight against Tuberculosis.

New recommendation for non-severe pulmonary TB and lymph node TB

5.1. Treatment shortening in children and adolescents with non-severe TB

Recommendation:

In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.

(Strong recommendation, moderate certainty of evidence)

Remarks

- **Non-severe TB** is defined as: **Peripheral lymph node TB; intrathoracic lymph node TB** without airway obstruction; **uncomplicated TB pleural effusion** or **paucibacillary, non-cavitary disease**, confined to **one lobe of the lungs**, and **without a miliary pattern**.
 - Children and adolescents who do not meet the criteria for non-severe TB should receive the standard six-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.
 - The use of ethambutol in the first two months of treatment is recommended in settings with a high prevalence of HIV,²⁶ or of isoniazid resistance.²⁷
-

And implementation...

Bring it to action

*“good care comes with
and from good science”*

*“but it’s the
implementation of
science that matters”*

Summary: paediatric TB from since to impact with less is more

Clinical presentation

Child-friendly testing

Short and easy to administer treatment

