The future of diagnostics for paediatric TB

Luis Cuevas
Liverpool School of Tropical Medicine

TB in children

- Statistics unreliable
  - Historical emphasis on reporting smear-positive patients
  - Difficult to confirm the diagnosis
  - Different clinical presentation

Up to 25% of cases in some high TB burden settings occur in children

1-1.4 million cases

Children

- Paucibacillary
- Less cavitations
- More disseminated disease
  - miliary TB,
  - EPTB,
  - bone,
  - abdominal,
  - glandular,
  - TBM
- Unable to expectorate
- Dependent on adults to attend a clinic

Non – sputum specimens

- Nasopharyngeal aspirate (NPA)
- Sputum induction (IS)
- Throat swabs
- Gastric aspirates (GA)
- Urine
- Stools
- Blood
- Fine needle aspiration biopsy

› Low volume
› most test optimised for sputum

- Diagnosis is difficult
- Perception that children
  - Respond well to treatment
  - Treatment has fewer side effects
- Confirmation of diagnosis considered less necessary

- Typically 5%-15% of cases confirmed
- Clinicians do not bother confirming cases
- Low numbers reported
- Child-friendly TB diagnostics receive low priority by
  - control programmes
  - researchers
  - test developers

Without proper diagnostics

- Difficult to define outcomes to assess
  - The magnitude of the problem
  - Prevalence of drug resistance
  - New drugs
  - New vaccines
  - Efficacy of control measures

"A high risk area for investment"

Current diagnostics

		Results	Sensitivity
Before 2007	ZN microscopy Solid Culture	2-3 days 30-60 days	
2007	**Liquid Culture / DST** **Rapid speciation**	8-30 days	+10% than LJ
2008	**Line Probe Assay** **(1st line, Rif & INH)**	2-4 days	For SM+
2009	**LED - FM**	1-2 days	+10% than ZN
	MODS, CRI, NRA	8-30 days	+10% than LJ
2010	**Xpert**	90 minutes	+40% than ZN

Have you heard of these tests?

What we hardly hear:

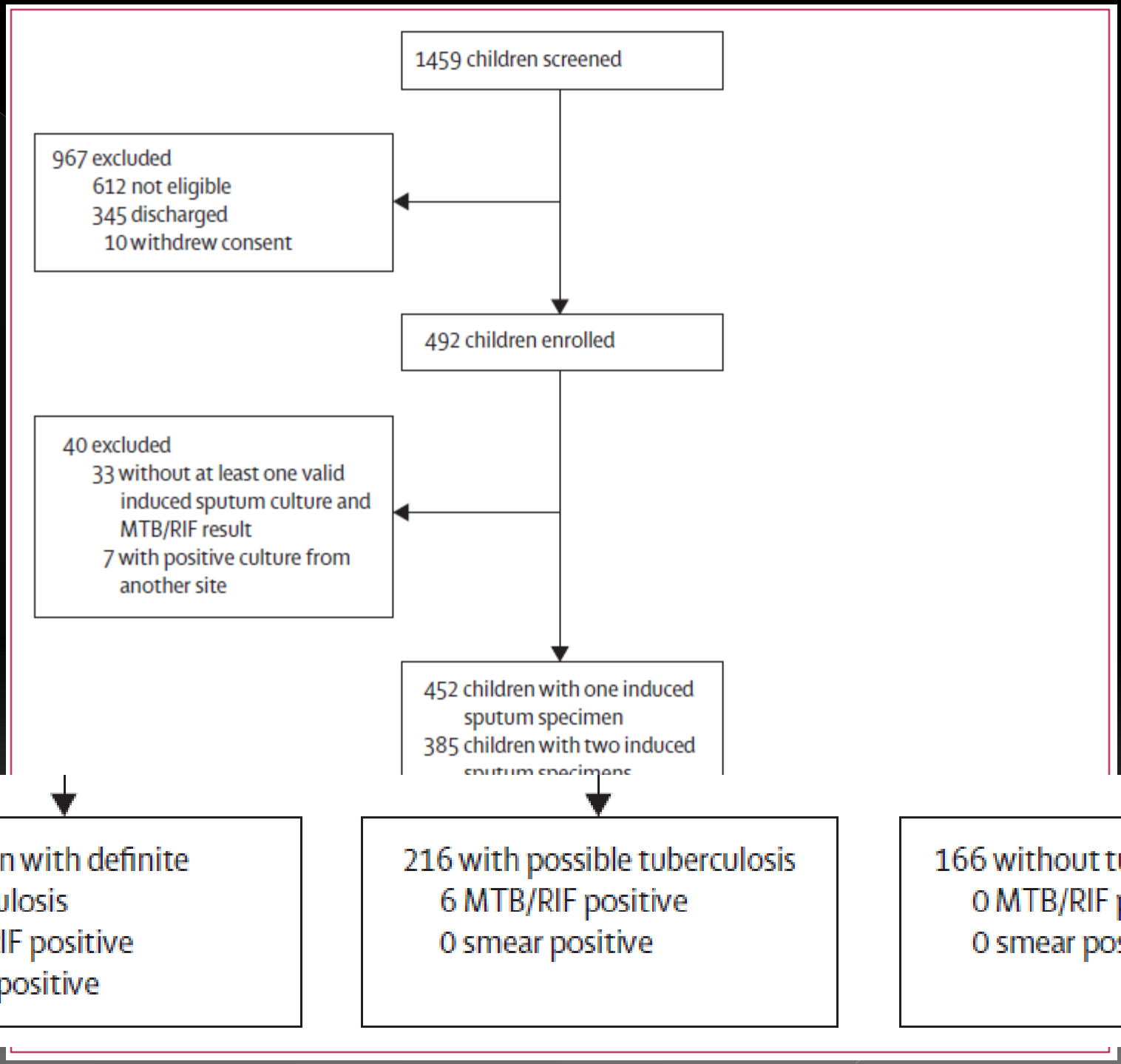
How do these tests perform in children?

Test	Publications		Performance in children
	Adults	Children	
Fine needle aspiration	> 6000	140	Potentially good. Most promising when combined with culture or NAAT
Fluorescence Microscopy (FM)	299	1	No data for LED-FM
LED-FM	33	0	
MODS	31	2	More sensitive than LJ. Duplicate GA for MODS was the best diagnostic test in one study
BACTEC 960	49	0	Anecdotic data suggest performance in children's sputum similar to adults
Fully automated BACTEC	13	0	
Line Probe assays	113	1	
LAMP	13	0	
Automated NAAT (Xpert)	32	1	

Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study

Mark P Nicol, Lesley Workman, Washiefa Isaacs, Jacinta Munro, Faye Black, Brian Eley, Catharina C Boehme, Widaad Zemanay, Heather J Zar

- 452 children
- Comparison with culture
- 70 (16%) positive culture
- 58 (13%) Xpert positive (2 x tests)
- (75% of culture confirmed)


1459 children screened
967 excluded
612 not eligible
345 discharged
10 withdrew consent
492 children enrolled
40 excluded
33 without at least one valid induced sputum culture and MTB/RIF result
7 with positive culture from another site
452 children with one induced sputum specimen
385 children with two induced
70 children with definite tuberculosis
52 MTB/RIF positive
27 smear positive
216 with possible tuberculosis
6 MTB/RIF positive
0 smear positive
166 without tuberculosis
0 MTB/RIF positive
0 smear positive

It is possible to do good quality research, but our house has been a bit messy

Poor diagnostics

Diagnosis rarely confirmed

Data difficult to interpret

Many algorithms

Studies not comparable

Different entry criteria

How to break this circle?

- Increase advocacy
- Consensus standard methods
  - Entry
  - Categories for diagnosis
  - Reporting

Advocacy

International Childhood Tuberculosis Meeting 2011

Stockholm, 17-18 March 2011

Stockholm declaration

Stop TB Partnership

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CALL TO ACTION for CHILDHOOD TB

Read the Call in French, Read the Call in Russian

Sign the Call to Action

We, participants gathered at the 'International Childhood Tuberculosis Meeting' held March 17-18, 2011 in Stockholm, Sweden recognize that:

Signed by more than 1000 individuals/organisations

Building consensus

- Stop TB Partnership – DEWG – Child TB
- NDWG
- NIH
- TDR
- Many individual researchers

Research methods

Evaluation of TB diagnostics in children:

1. **Proposed clinical case definitions for classification of intra-thoracic tuberculosis disease.**

2. **Methodological issues for conducting and reporting research evaluations of TB diagnostics for intrathoracic tuberculosis in children.**

Consensus from an Expert Panel*

- Standard analysis and reporting
- Explore alternative methods
  - whether the famous LCA could be applied.

Funding or research

- Conditional of using consensus case definitions
- Demonstrate high quality research is possible to stimulate funding and test evaluations in children.

The future – what is needed?

- Further evaluate new diagnostics – such as Xpert
  - A few studies underway
- Optimise tests to improve Mtb identification in non-sputum specimens
- Develop mechanisms to bring non POC tests to the child and feedback
  - Active case finding (e.g. TB Reach)
  - Contact tracing

Biomarkers

- Distinguish infection and disease
- Identify children at risk of disease progression after infection
- Methods to deliver these biomarkers to the POC

We are ready to start running. Are you?

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