

Improving TB Diagnosis in Children

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CDC-Kenya
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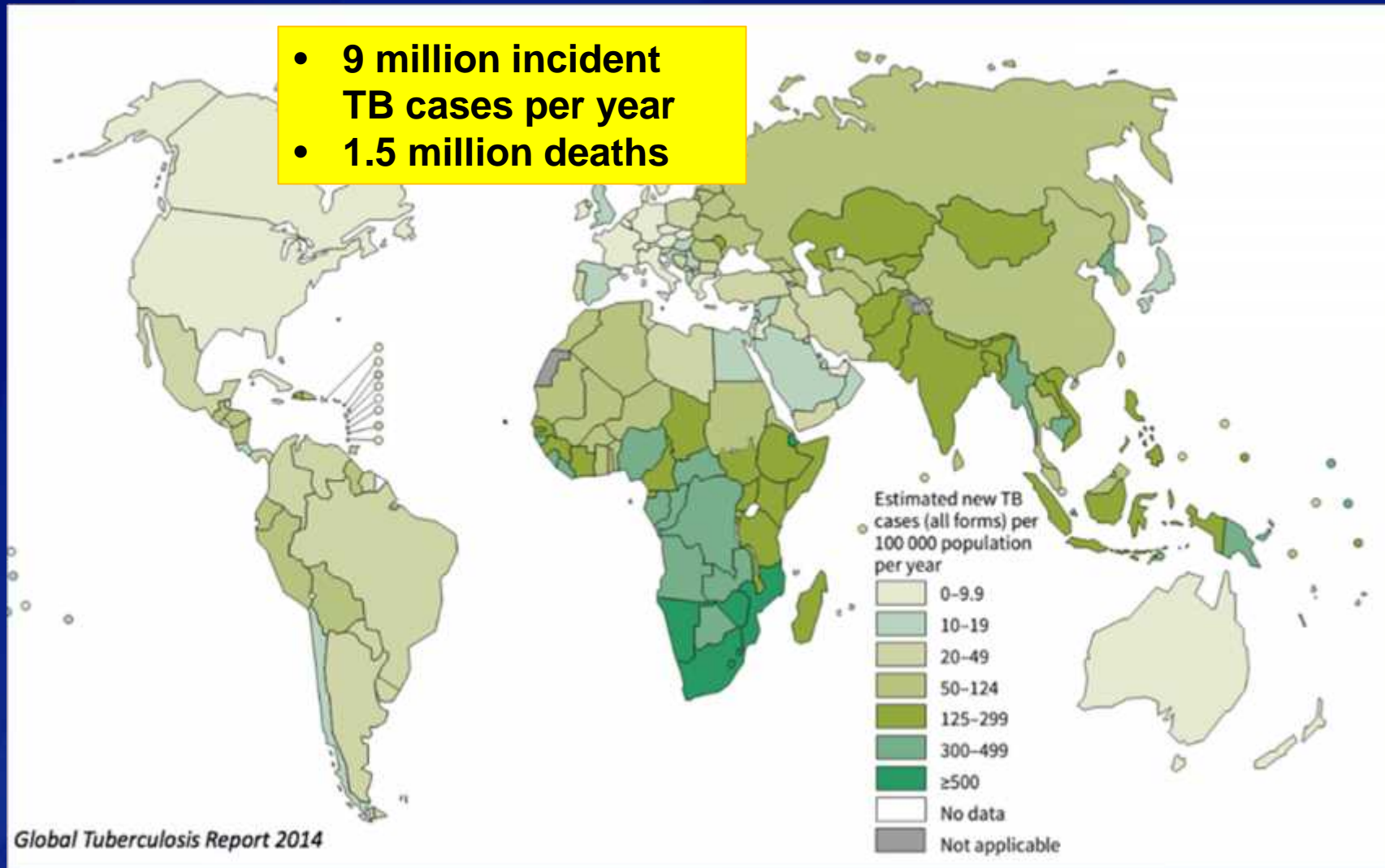


Center for Global Health
Division of Global HIV/AIDS



Global TB Incidence Rates

- 9 million incident TB cases per year
- 1.5 million deaths



Global Tuberculosis Report 2014

Pediatric TB: What is burden?

- No global estimates until 2012
- First WHO estimate:
 - 530,000 incident cases per year
 - “At least” 74,000 childhood TB deaths
- Major challenges due to
 - Insufficient diagnostic accuracy
 - Poor case detection

New Global Pediatric TB Estimates

Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates

*Helen E Jenkins, Arielle W Tolman, Courtney M Yuen, Jonathan B Parr, Salmaan Keshavjee, Carlos M Pérez-Vélez, Marcello Pagano, Mercedes C Becerra, * Ted Cohen**

- Most rigorous analytic effort to date
- Based on systematic literature and logistic regression models
- Estimated proportion of pediatric cases among all reported cases: 8-12%
- 1 million pediatric TB cases and 31,000 children with multidrug-resistant TB per year

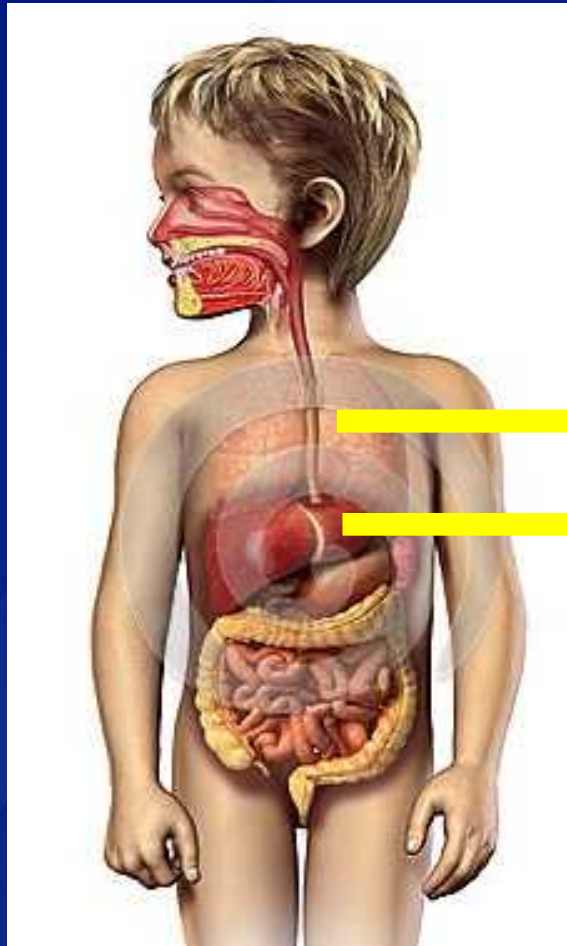
Clinical TB in Children

- Children highly susceptible to TB
- Often progress quickly to disease or death
- Clinical disease differs from adult-type disease
 - Paucibacillary disease
 - Extrapulmonary disease relatively more common
 - Subtle chest X-ray findings (cavitation rare)
 - Non-specific symptoms

Challenges of Diagnosis

- Young children unable to expectorate sputum
- Alternative specimens difficult to obtain
- Microscopy rarely diagnostic
- “Gold standard” of culture insensitive
- Imprecise clinical case definition

Recommended Specimens: Children <5



Induced sputum

Gastric aspirate

Recommended Specimens

- Gastric aspirate: Insertion of tube through nose to stomach, aspiration of fluid
- Induced sputum: Inhalation of hypertonic saline to induce coughing, nasopharyngeal suctioning of fluid

Gastric Aspirate and Induced Sputum



- Generally require hospitalization
- Require skilled medical staff and equipment
- Invasive, require restraint
- Rarely used in high-burden settings

Alternate Specimens and Tests

- Other tests have been studied
- Many studies of 1 test vs. another
 - IS vs. GA
 - Stool vs. IS and/or GA
 - Blood culture
- Limited to no evidence looking at broad range of specimens / tests, determining which combination best

Peds TB Study Main Objective

Identify the best possible combination of specimen types and diagnostic tests for TB diagnosis

Study Overview

- **Design: Prospective cohort study**
- **Population: Children <5 years of age**
- **Sick cohort: prolonged symptomatology despite treatment**
 - **Cough 4 weeks, malnutrition 3 weeks, cervical lymphadenopathy 4 weeks, fever 1 week**
 - **Parenchymal abnormalities on CXR**
- **Cohort of healthy controls enrolled (selected non-invasive testing only)**

Study Overview

- **Sick cohort**
 - **Admission for digital X-ray, physical examination, medical history, specimen collection**
 - **Follow-up at 2 weeks, 2 months, 6 months**
- **TB treatment and IPT as indicated**
- **Location: Kisumu, Kenya**
- **Collaboration between CDC, KEMRI and Harvard**
- **Funding mostly from USAID, also CDC, and others**

Specimen Collection (sick cohort)

Procedure	Test
2 nasopharygeal aspirates	Cx + Xpert
2 induced sputum	Cx + Xpert
2 gastric aspirates	Cx + Xpert
2 string tests	Cx + Xpert
2 stool specimens	Cx + Xpert
2 urine specimens	Cx + Xpert
1 lymph node FNA	Cx + Xpert
1 blood specimen	Cx

Clinical Case Definitions

SUPPLEMENT ARTICLE

Evaluation of Tuberculosis Diagnostics in Children: I. Proposed Clinical Case Definitions for Classification of Intrathoracic Tuberculosis Disease. Consensus From an Expert Panel

Stephen M. Graham,^{1,2} Tahseen Ahmed,³ Farhana Anwarullah,⁴ Reson Browning,⁵ Vicky Cardenas,⁶ Martina Casanighi,⁷ Luis E. Cuevas,⁸ Mariam Gale,⁹ Robert P. Gie,¹⁰ Malgorzata Grzeszka,¹¹ Ed Mandelzimas,¹² Mark Nathooil,¹³ Anuska C. Neening,¹⁴ Patrick Jean-Philippe,¹⁵ Beate Kempema,^{16,17} Sushil Kumar Kohra,¹⁸ Christian Lienhardt,¹⁹ Jennifer Lighter Fisher,²⁰ Shabir Madhi,²¹ Manodhara Makhsos,²² Sam J. Marks,²³ David F. McKeown,²⁴ Heather Menzies,²⁵ Charles Mitchell,²⁶ Sushil Modi,²⁷ Lynn Motwan,²⁸ Philippa Musso,²⁹ Sharon Nachman,³⁰ Clydette Pasmitt,³¹ Mona Rigaud,³² Vanessa Rivaire,³³ Jeffrey B. Starke,³⁴ Soanya Swaminathan,³⁵ and Claire Wagfield³⁶

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There is a critical need for improved diagnosis of tuberculosis in children, particularly in young children with intrathoracic disease as this represents the most common type of tuberculosis in children and the greatest diagnostic challenge. There is also a need for standardized clinical case definitions for the evaluation of diagnostics in prospective clinical research studies that include children in whom tuberculosis is suspected but not confirmed by culture of *Mycobacterium tuberculosis*. A panel representing a wide range of expertise and child tuberculosis research experience aimed to develop standardized clinical research case definitions for intrathoracic tuberculosis in children to enable harmonized evaluation of new tuberculosis diagnostic technologies in pediatric populations. Draft definitions and statements were proposed and circulated widely for feedback. An expert panel then considered each of the proposed definitions and statements relating to clinical

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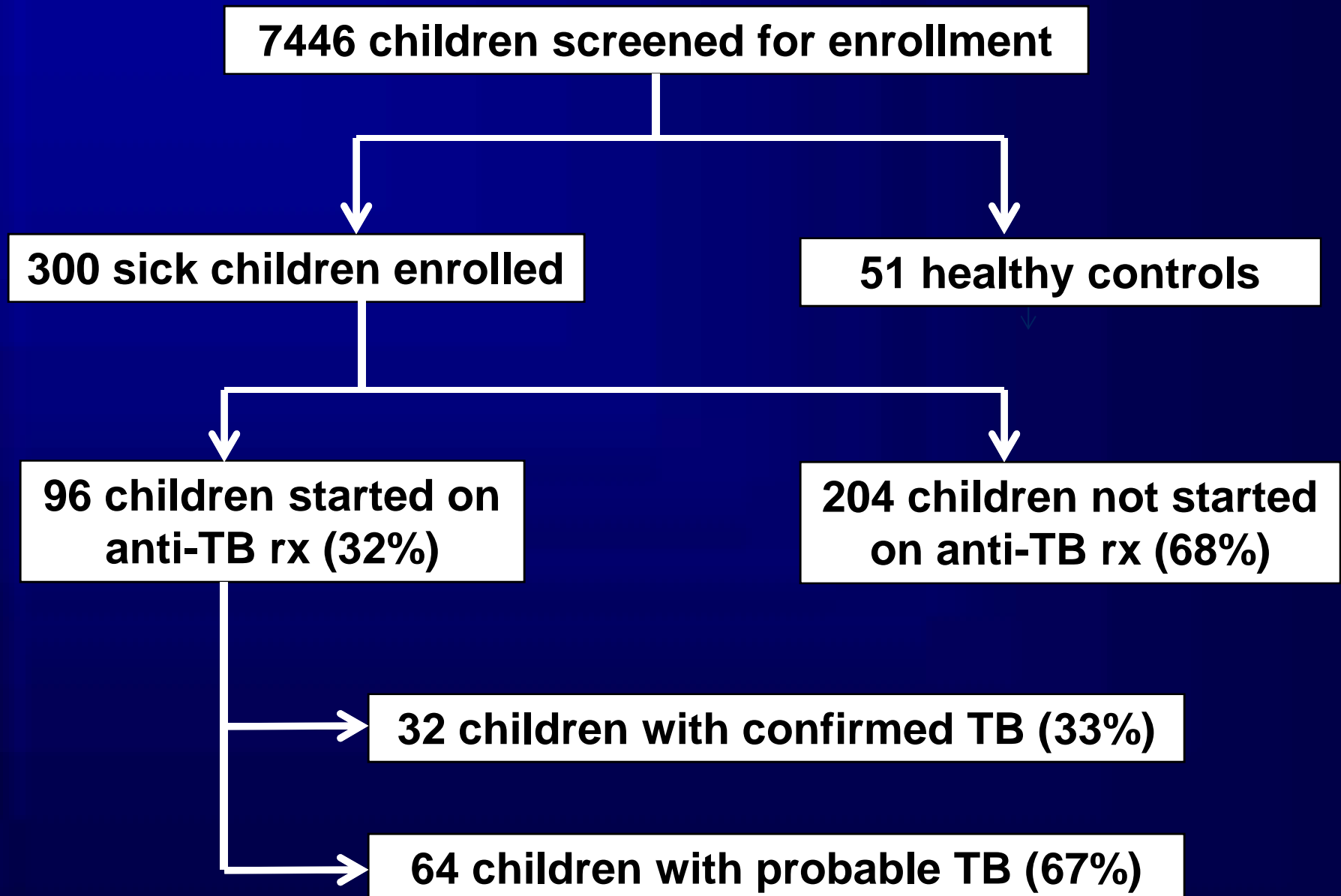
Intrathoracic Tuberculosis Definitions for Diagnostic Research in Children • JID 2012;205 (Supp 1)

SUPPLEMENT ARTICLE

Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children: An Update

Stephen M. Graham,^{1,2,3} Luis E. Cuevas,⁴ Patrick Jean-Philippe,⁵ Reson Browning,⁶ Martina Casanighi,⁷ Anuska C. Neening,⁸ Beate Kempema,^{9,10} Anuska C. Neening,¹¹ Anuska C. Neening,¹² Anuska C. Neening,¹³ Anuska C. Neening,¹⁴ Anuska C. Neening,¹⁵ Anuska C. Neening,¹⁶ Anuska C. Neening,¹⁷ Anuska C. Neening,¹⁸ Anuska C. Neening,¹⁹ Anuska C. Neening,²⁰ Anuska C. Neening,²¹ Anuska C. Neening,²² Anuska C. Neening,²³ Anuska C. Neening,²⁴ Anuska C. Neening,²⁵ Anuska C. Neening,²⁶ Anuska C. Neening,²⁷ Anuska C. Neening,²⁸ Anuska C. Neening,²⁹ Anuska C. Neening,³⁰ Anuska C. Neening,³¹ Anuska C. Neening,³² Anuska C. Neening,³³ Anuska C. Neening,³⁴ Anuska C. Neening,³⁵ Anuska C. Neening,³⁶ Anuska C. Neening,³⁷ Anuska C. Neening,³⁸ Anuska C. Neening,³⁹ Anuska C. Neening,⁴⁰ Anuska C. Neening,⁴¹ Anuska C. Neening,⁴² Anuska C. Neening,⁴³ Anuska C. Neening,⁴⁴ Anuska C. Neening,⁴⁵ Anuska C. Neening,⁴⁶ Anuska C. Neening,⁴⁷ Anuska C. Neening,⁴⁸ Anuska C. Neening,⁴⁹ Anuska C. Neening,⁵⁰ Anuska C. 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Study Results



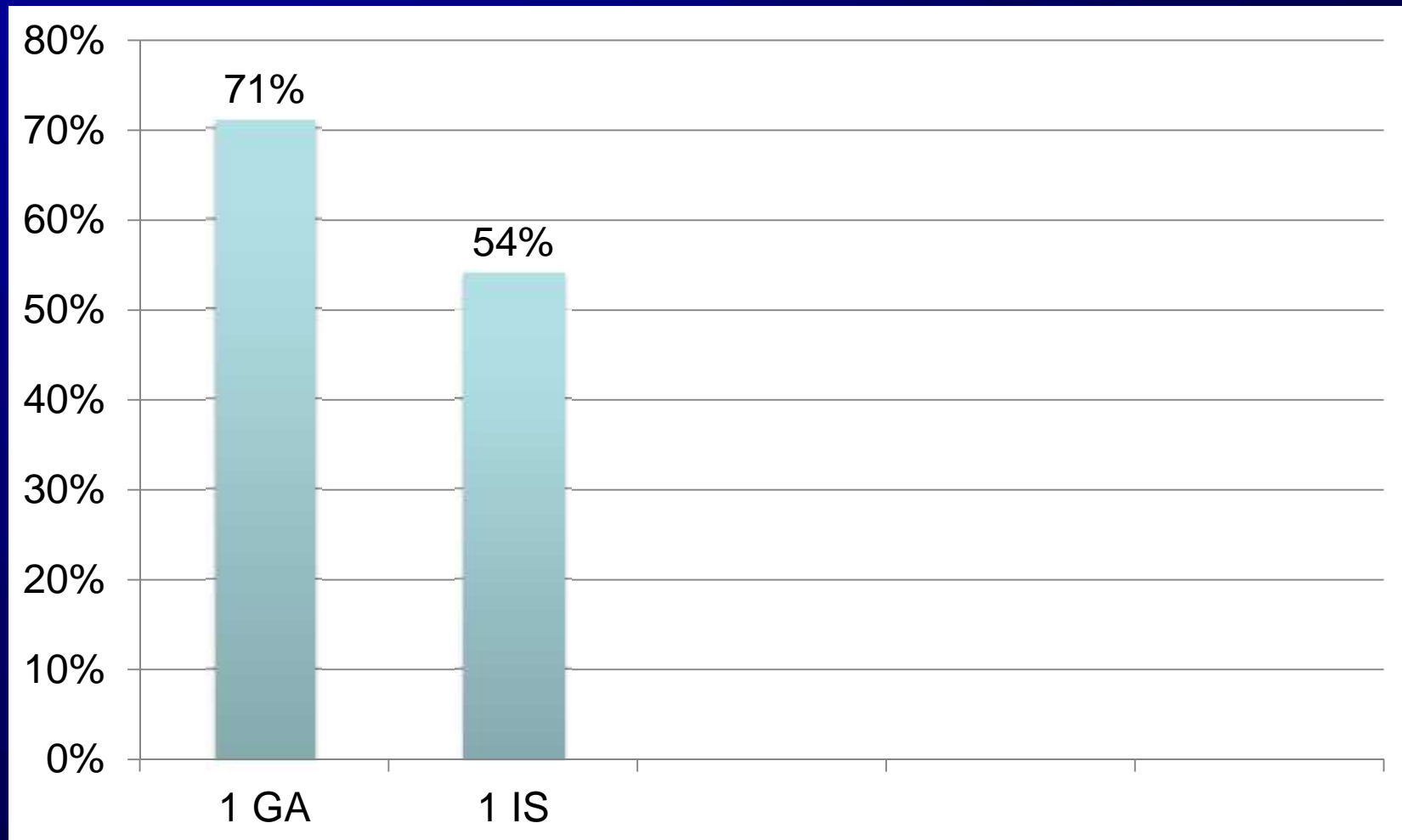
Cohort Characteristics

Characteristic	n	%
Median age in months (IQR)	25	(13-43)
Female gender	151	50
HIV infected	79	26
Severe malnutrition (< -3 WAZ)	66	22
Moderate malnutrition (>-3 to ≤2 WAZ)	27	9
Mild malnutrition (>-2 to ≤1 WAZ)	40	13
BCG vaccinated	291	97
Positive TST	39	15
Household TB exposure	96	32

Diagnostic Yield of Specimen Types (n=32)

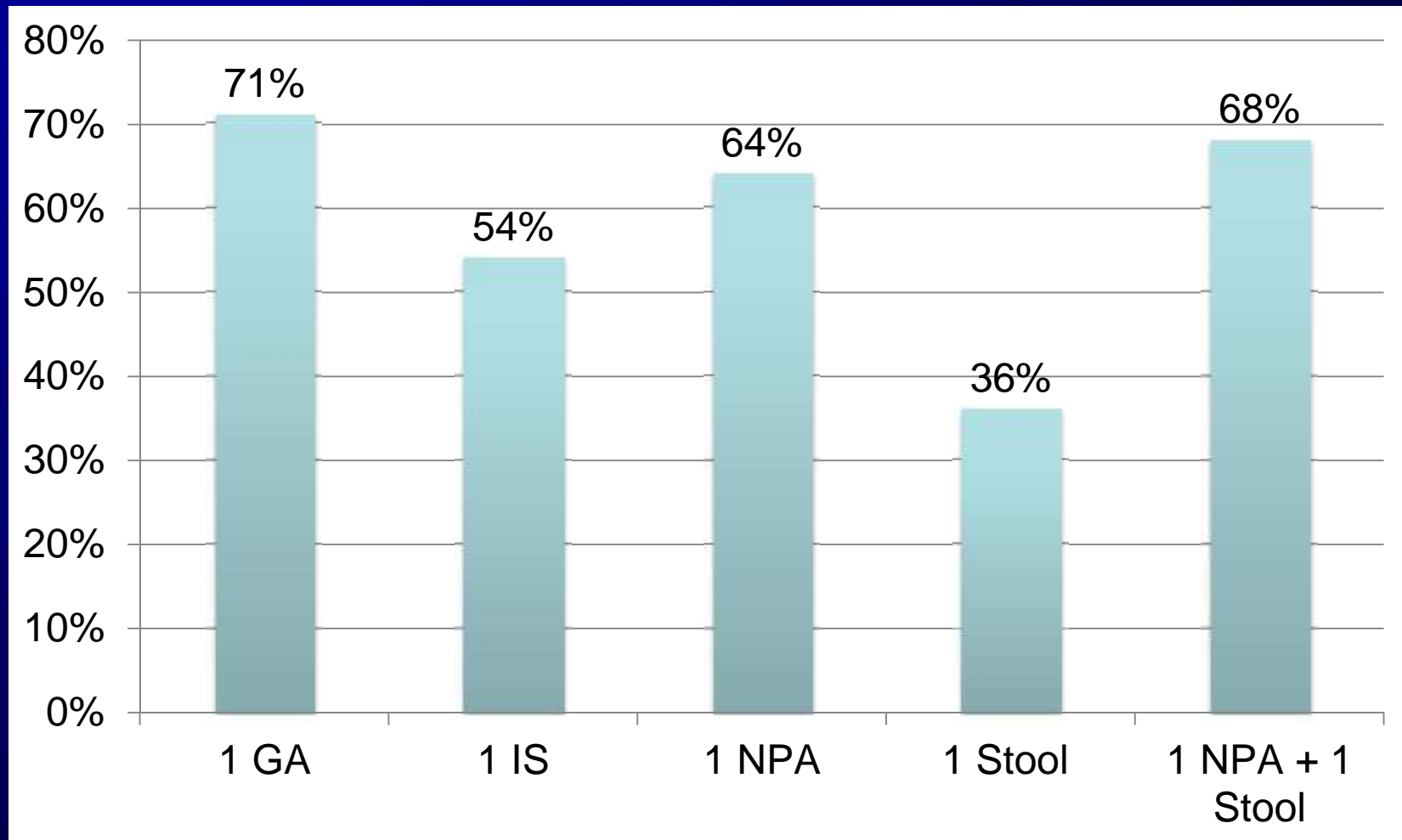
Specimen	Diagnostic Test		
	FM+	Cx +	Xpert +
Gastric Aspirate	20%	73%	53%
Nasopharyngeal Aspirate	19%	69%	53%
Induced Sputum	14%	66%	48%
String Test	10%	40%	37%
Stool	13%	23%	43%
Urine	3%	7%	14%
Blood	NA	7%	NA
LNA FNA	0%	21%	14%

Comparative Specimen Yield (n=28)



* Cx or Xpert positive; among children with available specimens

Comparative Specimen Yield (n=28)



* Cx or Xpert positive; among children with available specimens

Additional study aims / elements

- **Ancillary tests: evaluating TST, QFT (multiple versions), nutritional tests**
- **Co-infections: malaria, HIV, helminths, viral and bacterial respiratory pathogens**
- **Emerging diagnostics / biomarkers**
 - Evaluating breath test / electronic nose
 - Repository: extensive storage of specimens for biomarker-related testing
- **All of above useful because study has very robust gold-standard, collected non-invasive specimens on healthy controls also**

Breath-based diagnosis of TB

- Hippocrates: patients with TB have “distinct smell of breath”
- Volatile organic compounds emitted
- Rats trained to detect TB in sputum
- “Electronic nose” technology used for medical applications (e.g. cancer detection)



Aeonose



- First validation study in adults in Bangladesh
 - 85% sensitivity, 95% specificity
- No data on children

Electronic Nose: Urine Testing



- ❑ Detection of volatile organic compounds (VOCs) in urine
- ❑ VOCs interact with chemical compounds affixed to filter paper
- ❑ Specific pattern developed corresponding to MTB

Conclusions, next steps, program implications

- **TB culture on gastric aspirate with the highest diagnostic yield**
- **Identified combination of more easily obtainable specimens with yield comparable to commonly accepted gold standard (NPA + stool)**
 - Kenya may pilot this approach more broadly
- **Evidence also can support determining which tests to use in clinical trials**
- **Evaluations of emerging diagnostics could help to advance field of TB diagnostics in children**

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Thank You

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Center for Global Health
Division of Global HIV/AIDS



Other Tests

Test Type	Test	Sick cohort	Healthy controls
Ancillary	TST	Yes	Yes
	Quantiferon G-IT Assay	Yes	Yes
	Micronutrients assessment (sub-study)	Yes	Yes
	T Spot. TB (sub-study)	Yes	No
Emerging	Immunomodulated Quantiferon	Yes	Yes
	QFT Plus	Yes	Yes
	Breath testing (electronic nose)	Yes	Yes
Co-Infection	HIV, malaria, helminths	Yes	Yes
	Respiratory viral and bacterial infections	Yes	No

Biomarker Diagnostics

Specimen	Host-based	Pathogen-based
Breath	Electronic nose for volatile organic compounds (VOCs)	
Urine	Electronic nose for VOC detection	
Urine	Proteomics	ELISA-based peptide detection
Urine	Cytokine/Chemokine profiling	
Blood	Proteomics	
Blood	Transcriptomics	
Blood	Novel IFN- assays	
Blood	Cytokine/Chemokine profiling	
OP swab		Multiplex PCR, Metagenomics
NP swab		Multiplex PCR, Metagenomics
Gastric aspirate		Multiplex PCR, Metagenomics

Repository Specimens

Specimen	# of Aliquots	Sick Cohort	Healthy Controls
Plasma	4	Yes	Yes
QFT supernatant (TB Ag/Nil)	4	Yes	Yes
Serum	4	Yes	Yes
Whole blood (Paxgene)	1	Yes	Yes
Urine (standard collection)	7	Yes	Yes
Urine (nucleic acid storage)	1	Yes	No
Stool (standard collection)	2	Yes	Yes
Stool (nucleic acid storage)	2	Yes	Yes
NP swab (nucleic acid storage)	1	Yes	No
OP swab (nucleic acid storage)	1	Yes	No
Gastric aspirate (nucleic acid storage)	1	Yes	No
PBMCs (sub-study)	1	Yes	No

Global Pediatric TB

- Deadly
- Vastly under-diagnosed, true burden unknown
- No good diagnostic test
 - *“Gold standard” culture positive in <10-30% cases*
- Preventable and treatable

Emerging Diagnostic Tests

- Detect biomarkers of disease or infection
 - Host-specific
 - Bacteria-specific
 - Both host and bacteria
- Evaluate performance characteristics

A Blueprint to Address Research Gaps in the Development of Biomarkers for Pediatric Tuberculosis

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Childhood tuberculosis contributes significantly to the global tuberculosis disease burden but remains challenging to diagnose due to inadequate methods of pathogen detection in paucibacillary pediatric samples and lack of a child-specific, reliable biomarker to identify disease. Accurately diagnosing tuberculosis in children is required to improve case detection, surveillance, health-care delivery, and otherwise advance. In May 2014, the National Institutes of Health convened a workshop including researchers in the field to delineate priorities to address this research gap. This blueprint describes the consensus from the workshop, identifies critical research steps to advance this field, and aims to catalyze efforts toward harmonization and collaboration in this area.

Keywords: tuberculosis; children; diagnosis; biomarkers; blueprint

Childhood tuberculosis is estimated to account for 6% of the tuberculosis burden globally, and for 4%–21% of the caseload in the 24 high-incidence countries that account for 80% of global tuberculosis cases [1]. Mathematical modeling suggests that only 35% of tuberculosis cases in children are detected [2]. Improving the accuracy of tuberculosis diagnosis in children is required to improve case detection and ultimately, surveillance,

efficiency of health-care delivery, future research, and effective advocacy.

However, obtaining an accurate diagnosis in children in tuberculosis endemic settings remains challenging. There is overlap of the clinical presentation of tuberculosis with other common childhood diseases such as parasitic, human immunodeficiency virus (HIV)-associated lung disease, and severe malnutrition [3]. Clinical and chest radiographic features are often nonspecific and subject to variable interpretation [4]. Structured diagnostic scoring systems based on clinical and radiographic findings and tuberculosis testing (growth variability in case yield) with poor agreement between scoring systems [5]. Microbiological confirmation is possible in children of all ages, but is rarely attempted due to procedural difficulties in obtaining respiratory specimens.

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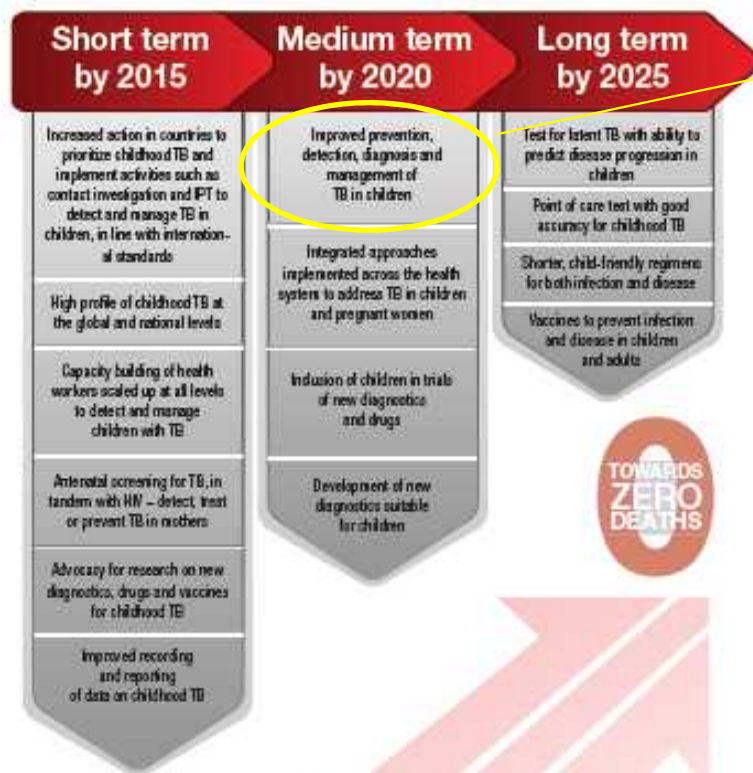
Child TB Research

- Identified as priority area of focus by WHO, International Union of TB and Lung Disease, Stop TB Partnership
- No previous comprehensive evaluation of specimens and tests for diagnosis
- Improved diagnostics urgently needed
 - Clinical care
 - Clinical and vaccine trials

ROADMAP FOR CHILDHOOD TUBERCULOSIS



TIMELINE: KEY ACTIONS TO ADDRESS CHILDHOOD TB



Improved Diagnostics

For further information contact:
 Global TB Programme
 World Health Organization
 20 Avenue Appia
 1211 Geneva 27
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 Website: www.who.int/tb

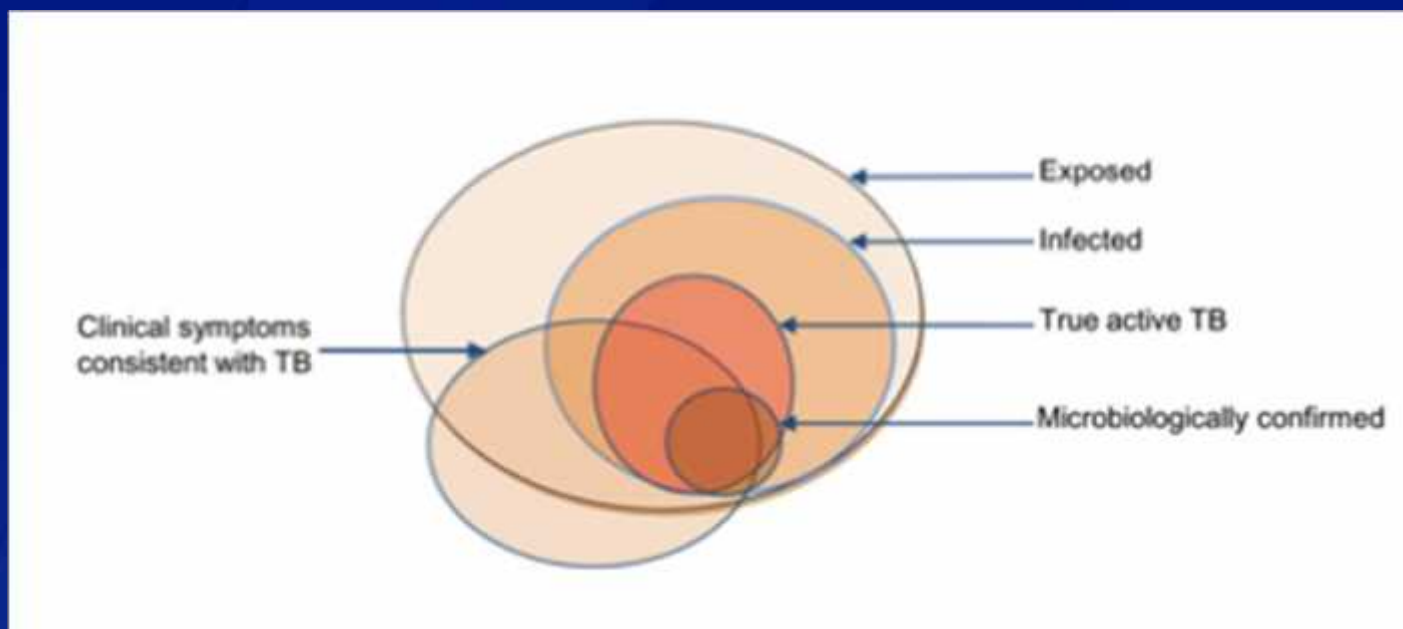


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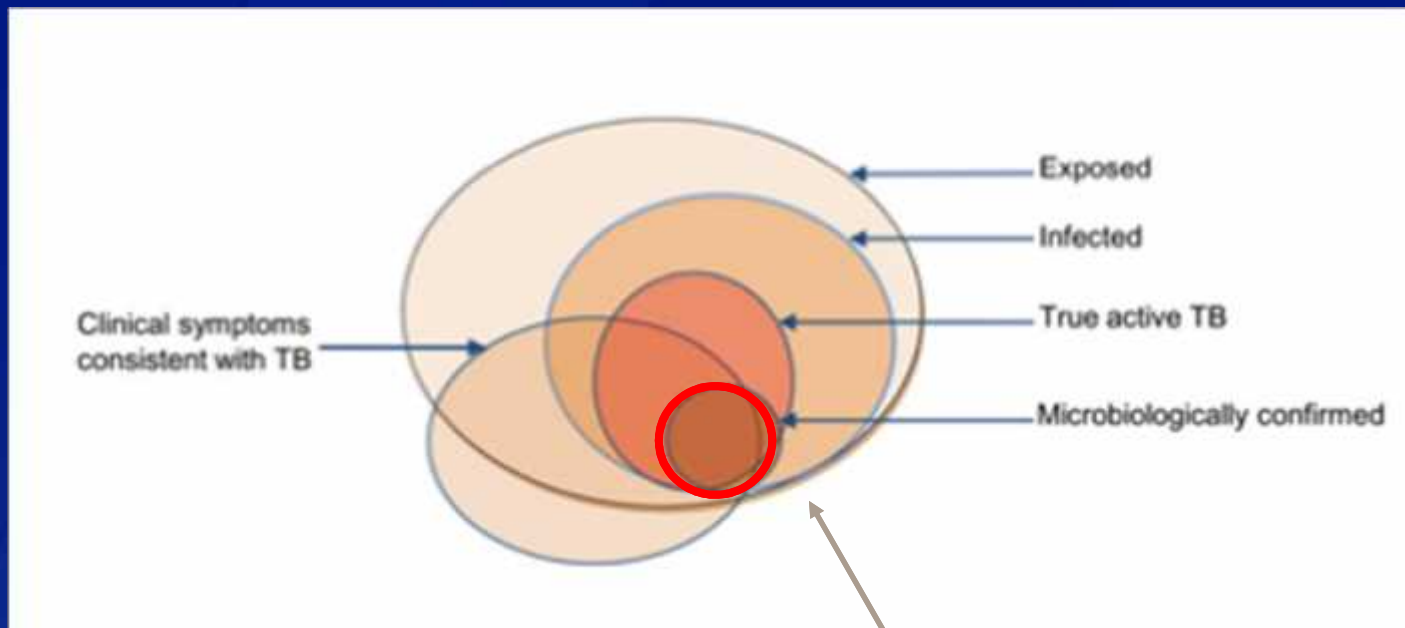


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TB in Children: The Challenge

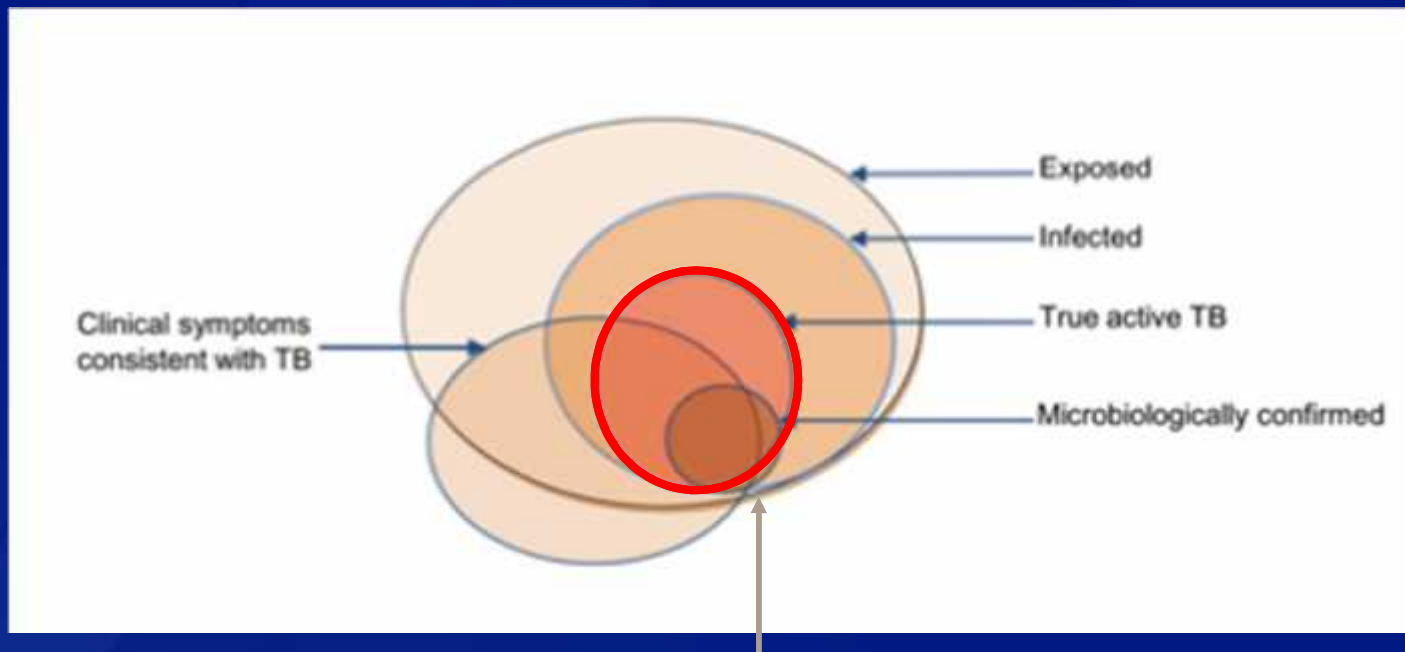


Goals for Improved Diagnostics



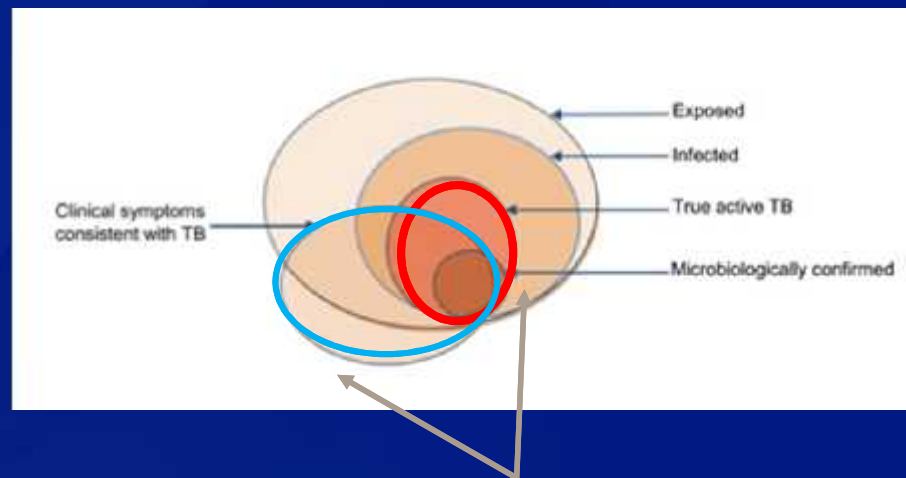
**More feasible specimens and tests
for bacteriologic diagnosis**

Goals for Improved Diagnostics



New diagnostic tests to increase proportion of children with confirmed disease

Goals for Improved Diagnostics



Screening tests to rule out TB

Kenya TB Study Objectives

- Identify the best possible combination of specimen types and diagnostic tests for TB diagnosis
- Determine a feasible and sensitive combination of specimen types and tests
- Characterize the diagnostic performance of biomarkers for TB
- Determine impact of co-infections, immunologic status and micronutrient deficiencies on performance of biomarkers

Study Overview

- Design: Prospective cohort study
- Population: Children <5 years of age
 - HIV infected, uninfected, exposed
 - High suspicion for TB and high likelihood of culture-confirmed TB (*sick cohort*)
 - Asymptomatic children (*healthy controls*)
- Location: Kisumu, Kenya
- Collaboration: KEMRI, CDC, Harvard
- Funded by USAID + CDC

Enrolment Arms

- TB clinic
- Outpatient
- Inpatient
- TB contacts
- Healthy controls

Enrolment Criteria

Enlarged cervical LN (>1cmx1cm) not responding to standard therapy

OR

Cough >28 days including 2 weeks after antibiotics OR
(inpatient only) pneumonia not responding to 5 days antibiotics

OR

Moderate or severe malnutrition not resolving with 3 weeks standard treatment

OR

Fever > 7 days not responding after 5 days with standard antibiotic or antimalarial treatment

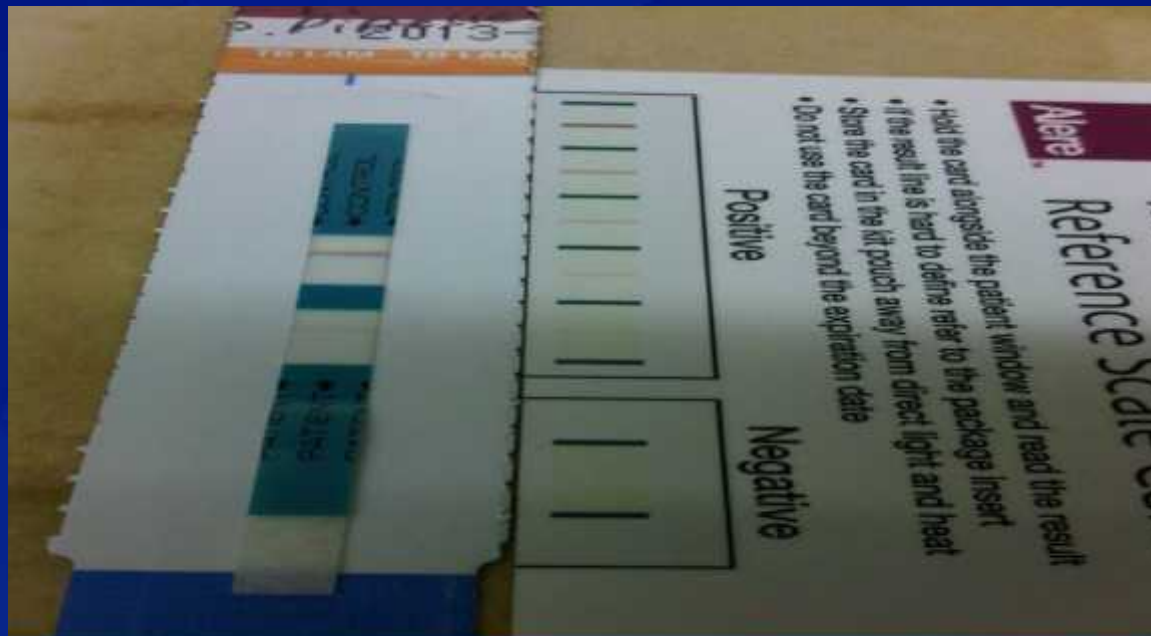
AND

Abnormal chest X-ray with parenchymal disease

Study Procedures

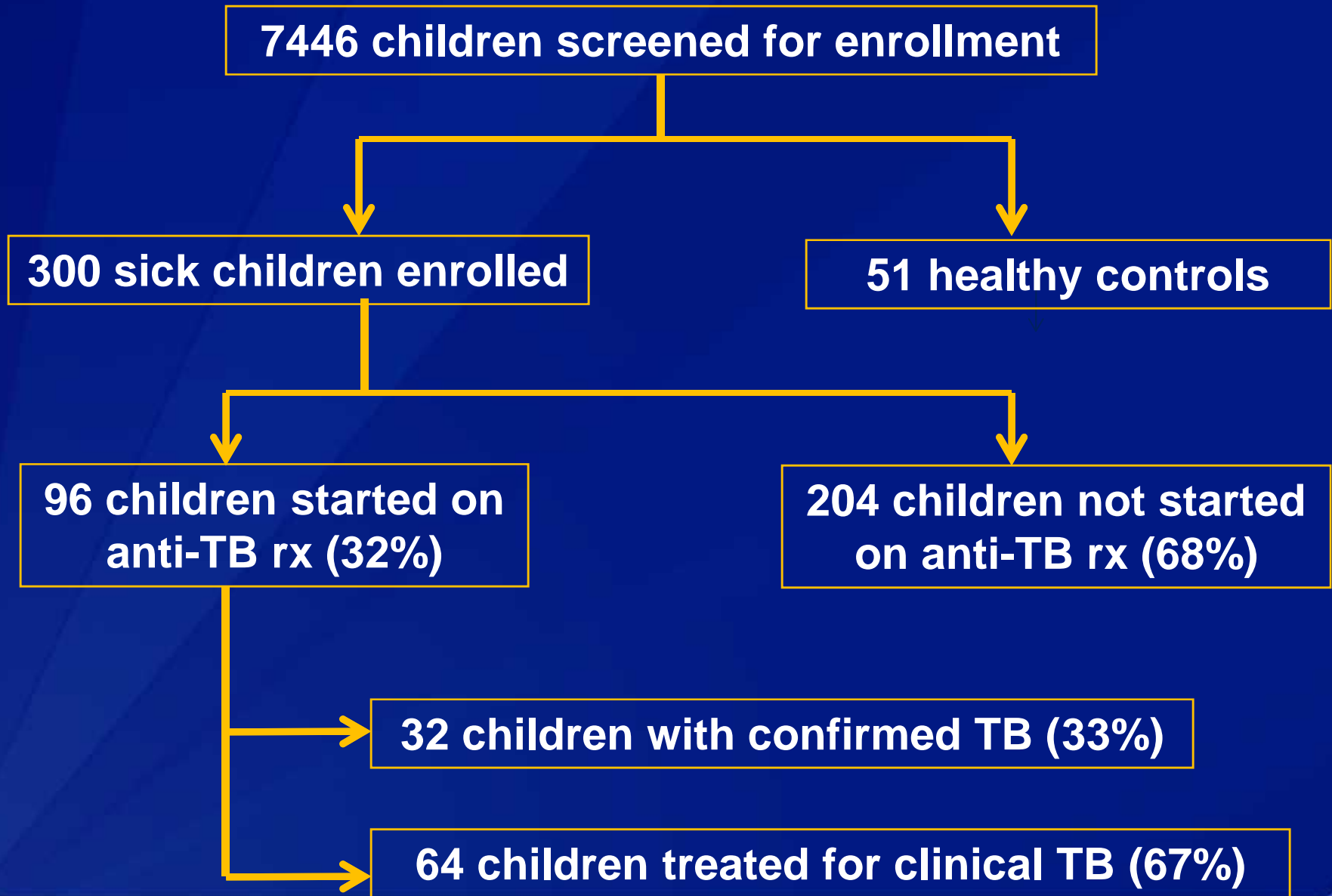
- Sick cohort
 - Admission for digital X-ray, physical examination, medical history, specimen collection
 - Follow-up at 2 weeks, 2 months, 6 months
- TB treatment and IPT as indicated
- Standard research clinical case definitions for analysis

TB LAM Antigen Assay

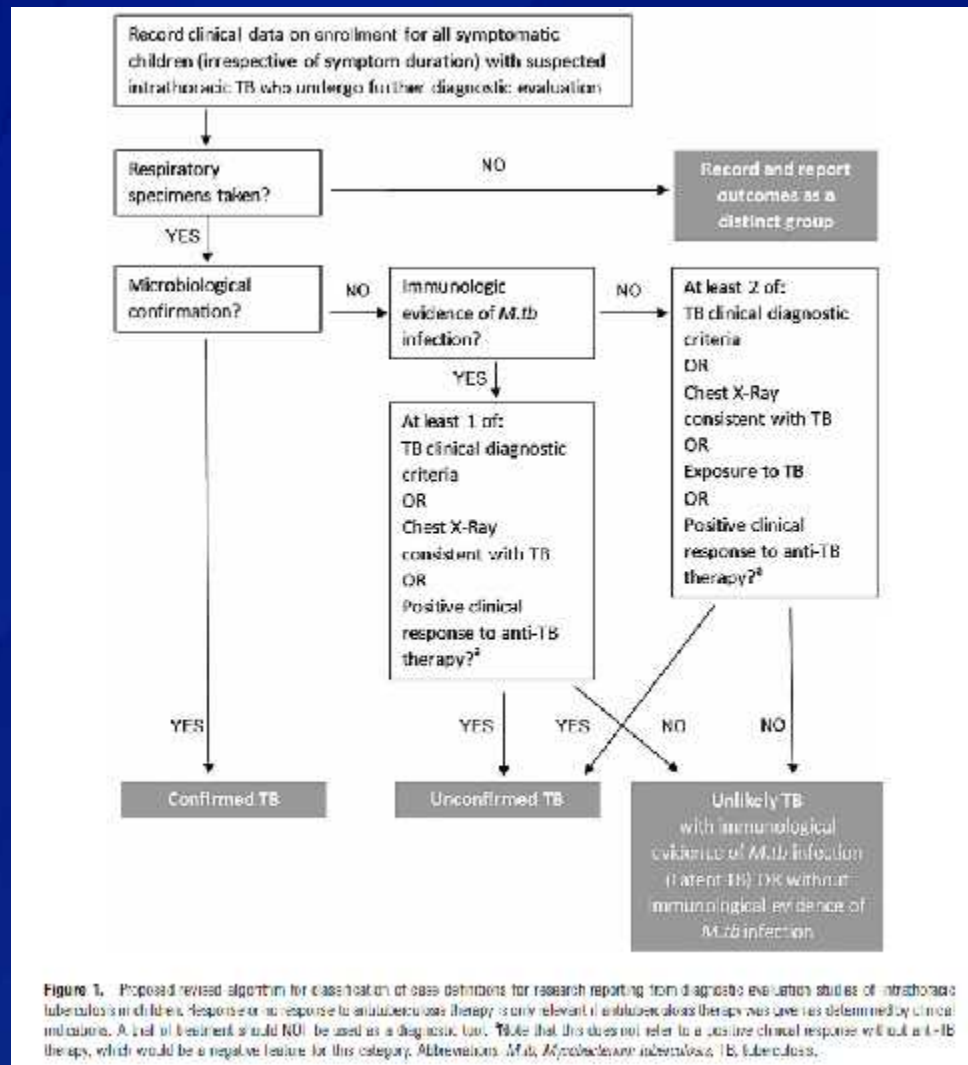


- ❑ Detects lipoarabinomannan (LAM) antigen in human urine
- ❑ Relatively sensitive (~67%) test in adults with TB/HIV (CD4<50)
- ❑ Limited data in children

Study Results



Case Classification



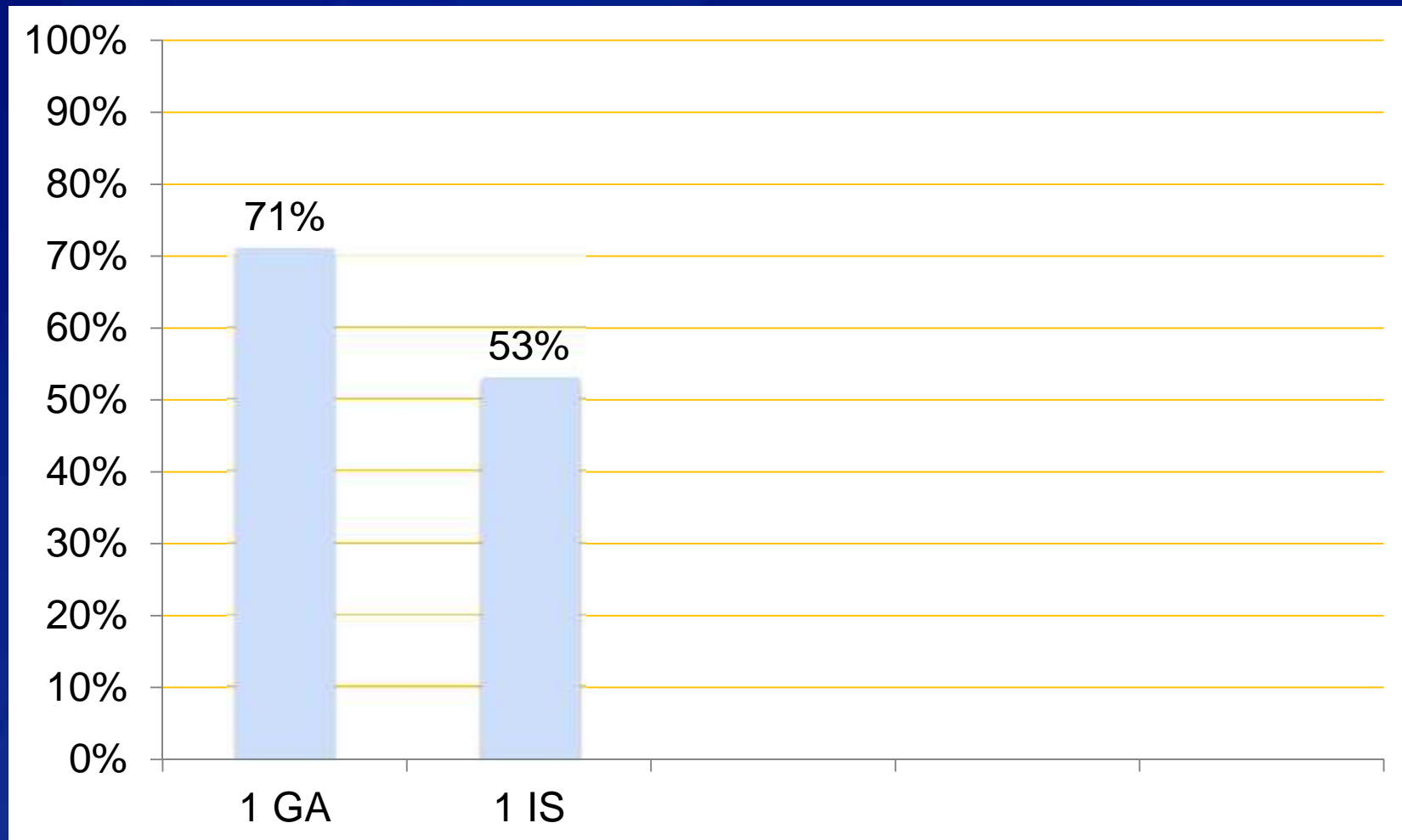
Specimens and Bacteriologic Tests (Sick Cohort)

Procedure	Test
2 nasopharygeal aspirates	Cx + Xpert
2 induced sputum	Cx + Xpert
2 gastric aspirates	Cx + Xpert
2 string tests	Cx + Xpert
2 stool specimens (3 additional)	Cx + Xpert (Xpert)
2 urine specimens	Cx + Xpert
1 lymph node FNA	Cx + Xpert
1 blood	Cx

Diagnostic Yield of Specimen Types (n=32)

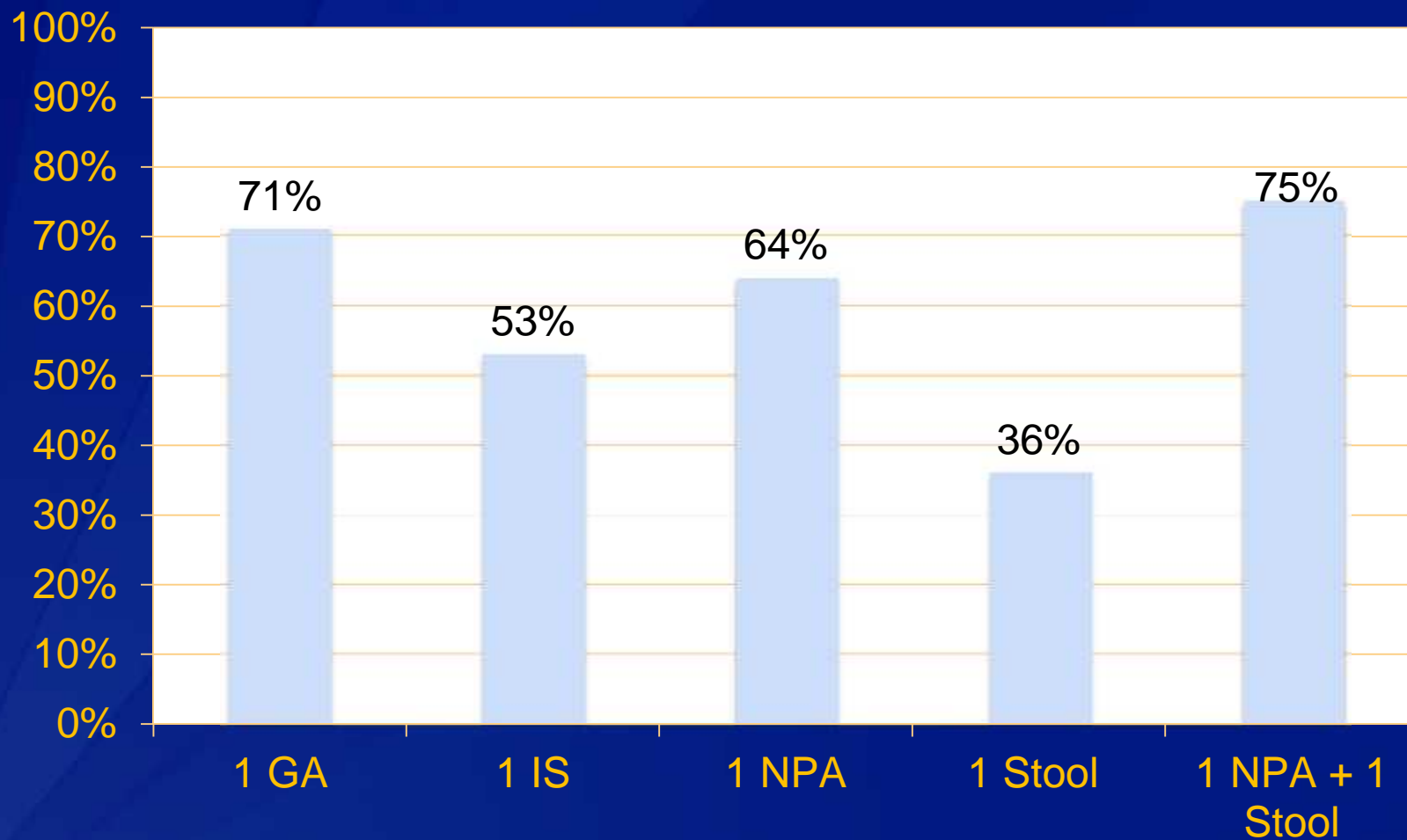
Specimen	Diagnostic Test		
	FM+	Cx +	Xpert +
Gastric Aspirate	20%	73%	53%
Nasopharyngeal Aspirate	19%	69%	53%
Induced Sputum	14%	66%	48%
String Test	10%	40%	37%
Stool	13%	23%	43%
Urine	3%	7%	14%
Blood	NA	7%	NA
LNA FNA	0%	21%	14%

Gold Standard Specimen Yield (n=28)



* Cx or Xpert positive; among children with available specimens

Comparative Specimen Yield (n=28)



* Cx or Xpert positive; among children with available specimens

Conclusions

- **TB culture on gastric aspirate has single highest diagnostic yield but difficult to obtain sample**
- **Combination of more easily obtainable specimens (stool and NPA) has yield comparable to gastric aspirate**
- **Next steps:**
 - **Ongoing analysis to determine best possible combination for research and clinical purposes**
 - **Ongoing work on evaluation of biomarkers**