Closing the Gap in TB Diagnosis in Children

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TB MAC Meeting
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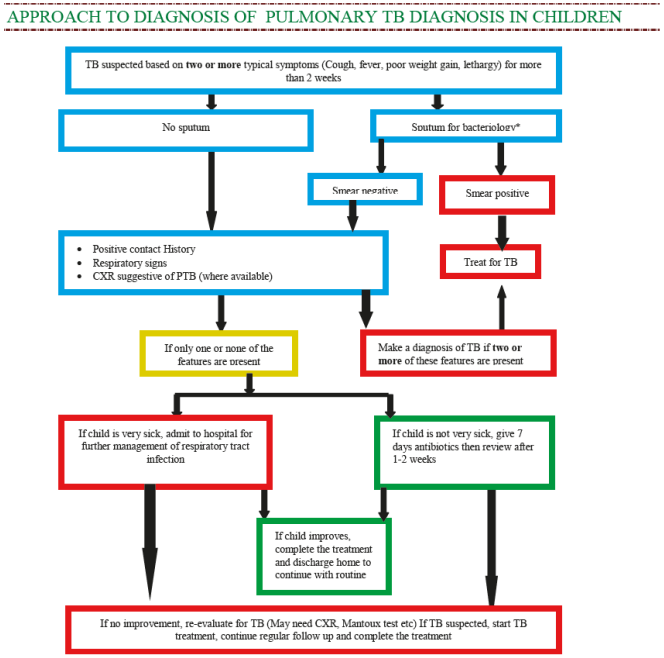
TB Disease in Young Children Globally

- Estimate 1 million childhood TB cases/year (~half <5 years)
- Most never diagnosed and treated
- Most cases that are diagnosed are “clinical” and not bacteriologically confirmed

Diagnosis of TB Disease in Young Children: Challenges

- **Bacteriologic diagnosis**
  - Low bacterial load (paucibacillary disease)
  - Lack of readily obtained specimens
- **Clinical diagnosis**
  - No strict diagnostic criteria
  - Clinical features (e.g., fever, cough, wasting, lymph nodes) common in other childhood illnesses
  - Subtle chest X-ray findings
  - Based on longitudinal assessment



Guidelines for Management of Tuberculosis and Leprosy in Kenya, July 2013 Edition.

Filling in the Diagnostic Gap: "Clinical" Disease

SUPPLEMENT ARTICLE

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 host biomarker to identify disease. Accurately diagnosing tuberculosis in children is required to improve case detection, surveillance, healthcare delivery, and effective advocacy. 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; biomarker; blueprint.

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Evaluation of Biomarker-based Tests

SUPPLEMENT ARTICLE

Evaluation of Tuberculosis Diagnostics in Children: 1. Proposed Clinical Case Definitions for Classification of Intrathoracic Tuberculosis Disease. Consensus From an Expert Panel

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

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SUPPLEMENT ARTICLE

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

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Consensus case definitions for childhood tuberculosis have been proposed by an international expert panel, aiming to standardize the reporting of cases in research focusing on the diagnosis of intrathoracic tuberculosis in children. These definitions are intended for tuberculosis diagnostic evaluation studies of symptomatic children with clinical suspicion of intrathoracic tuberculosis, and were not intended to predefine inclusion criteria into such studies. Feedback from researchers suggested that further clarification was required and that these case definitions could be further improved. Particular concerns were the perceived complexity and overlap of some case definitions, as well as the potential exclusion of children with acute onset of symptoms or less severe disease. The updated case definitions proposed here incorporate a number of key changes that aim to reduce complexity and improve research performance, while maintaining the original focus on symptomatic children suspected of having intrathoracic tuberculosis. The changes proposed should enhance harmonized classification for intrathoracic tuberculosis disease in children across studies, resulting in greater comparability and the much-needed ability to pool study results.

Keywords. childhood tuberculosis; tuberculosis classification; tuberculosis case definitions; tuberculosis diagnosis.

Tuberculosis is an important cause of morbidity and mortality in children in tuberculosis-endemic settings [1]. The World Health Organization (WHO) estimated that there were a total of 550 000 childhood tuberculosis cases globally in 2013 [2]. Due to acknowledged limitations of case detection and underreporting, these figures likely underestimate the true burden of childhood tuberculosis [3]. The WHO estimated that there were 80 000 deaths in children due to tuberculosis in 2013, an estimate that only included human immunodeficiency virus (HIV)–uninfected children [4]. Although there are no data of the numbers of tuberculosis-related deaths in HIV-infected children, the greatly increased risks of tuberculosis and of tuberculosis-related mortality in HIV-infected children compared with HIV-uninfected children are well established [4–6].

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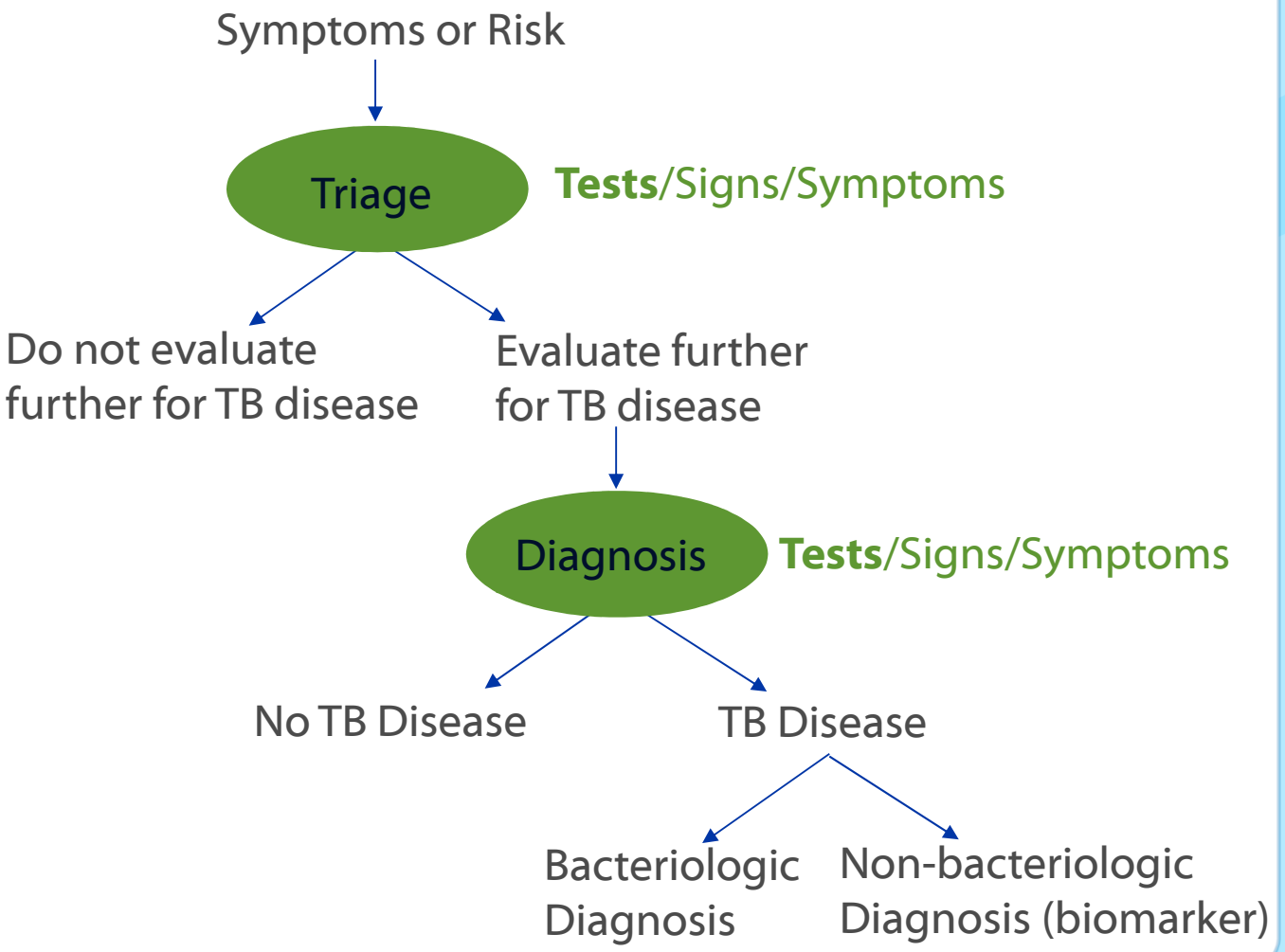
Slide 5

CS(13 make bigger the images

Cookson, Susan (CDC/CGH/DGHT), 9/10/2018

CS(8
CS(9

Simplified Algorithm for Diagnosis of Disease



Slide 6

CS(8 not sure why presenting this one now
Cookson, Susan (CDC/CGH/DGHT), 9/10/2018

CS(9 should you not have an arrow for just biomarkers - could be non-bacteriologic but biomarker positive
Cookson, Susan (CDC/CGH/DGHT), 9/10/2018

TB Diagnostics Study Goals

- Determine best combination of specimens and tests for bacteriologic diagnosis
- Evaluate performance of biomarker-based tests
- Determine the impact of co-infections and malnutrition on performance of diagnostic tests

Develop improved approach for screening and diagnosis of TB disease

Study Overview

- **Prospective cohort study children <5 years of age**
- **300 symptomatic children: prolonged symptomatology despite treatment for other causes**
  - Cough > 4 weeks, malnutrition >3 weeks, cervical lymphadenopathy > 4 weeks, fever > 1 week
  - Parenchymal abnormalities on CXR
- **50 healthy controls (asymptomatic): non-invasive testing only**
- **TB treatment and TB preventive therapy as indicated**
- **Location: Kisumu, Kenya**
- **Collaboration between Kenya Medical Research Institute (KEMRI), CDC, Harvard**

Study Procedures

Time Point	Procedure	Details
Baseline	Clinical Evaluation	Symptoms and physical findings Nutritional assessment Digital chest X-ray
	Bacteriologic diagnostic testing	Specimen collection Diagnostic tests
	Biomarker testing	Specimen collection Biomarker testing
	Co-infection testing	HIV, malaria, schistosomiasis, viral respiratory pathogens
	Nutritional testing	Blood micronutrient tests
	Repository specimen collection	Plasma, serum, whole blood (PAXgene), urine and stool, NP swabs, OP swabs, gastric aspirate
Follow-up (2 weeks, 2 months, 6 months)	Clinical Evaluation	Symptoms and physical findings Nutritional assessment

Tests and Specimens for Bacteriologic Diagnosis

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 fine needle aspirate	Cx + Xpert
1 blood specimen	Cx

* Symptomatic cohort only

Tests and Specimens for Biomarkers

Specimen	Host-based	Pathogen-based
		Tuberculin skin test (TST)
Breath	Electronic nose for detection of volatile organic compounds (VOCs)	
Urine		Electronic nose for VOC detection
Urine	Proteomics	ELISA-based peptide detection
Urine	LAM	
Urine	Cytokine/Chemokine profiling	
Blood	Proteomics	
Blood	Transcriptomics	
Blood	Standard and immunomodulated IFN-γ assays	
Blood	Cytokine/Chemokine profiling	
OP swab		Multiplex PCR, Metagenomics
NP swab		Multiplex PCR, Metagenomics
Gastric asp		Multiplex PCR, Metagenomics

Preliminary Study Results

300 symptomatic children enrolled

↓

~1/3 treated for TB disease

↓

~1/3 bacteriologically confirmed

~ 2/3 not bacteriologically confirmed

* Citations, references, and credits

Diagnostic Yield of Specimen Types (n=32)

	Smear Microscopy	Xpert or MGIT
Gastric Aspirate	5	22
NP Aspirate	6	22
Induced Sputum	4	15
String Test	2	13
Stool	4	14
LNA		3
Urine	1	4
Blood		1

Diagnostic Yield of Specimen Types (n=32)

Reference standard	
2 IS	20
1 GA + 1 IS	24
2 GA	24
Minimally invasive	
1 NPA	22
2 NPA	24
1 NPA + 1 stool	25
Invasive	
1 NPA + 1 GA	27
2 NPA + 2 GA	29
1 NPA + 2 GA + 1 stool	30

Diagnostic Yield of Specimen Types (n=32)

Reference standard	
2 IS	20
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Invasive	
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2 NPA + 2 GA	29
1 NPA + 2 GA + 1 stool	30

Preliminary Conclusions: Bacteriologic Diagnosis

- A combination of minimally-invasive specimens (nasopharyngeal aspirate and stool) had same yield as invasive gold-standard specimens (induced sputum or gastric aspirate) [utility: routine programmatic settings]
- Bacteriologic diagnosis may be improved by using a combination of invasive and non-invasive specimens [utility: concern for drug resistance, clinical trials]
- Despite extensive sampling and testing, a large proportion of TB disease not bacteriologically confirmed

Next Steps

- Evaluating combination of stool and NPA under programmatic conditions
- Evaluating biomarker-based tests against research clinical case definition
- Evaluating impact of co-infections and nutritional status on performance of diagnostic tests
- Developing an improved algorithm for TB diagnosis in children

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