Diagnostics for pediatric TB and harmonization of research on pediatric biomarkers

Devasena Gnanashanmugam, M.D.
Maternal, Adolescent & Pediatric Research Branch
DAIDS/NIAID/NIH

National Institute of Allergy and Infectious Diseases

Overview

- Background
- Prioritizing research questions
- Designing the Repository: Pediatric TB Diagnostics biobank consortium
- Sample/ Specimen Collection
- Data Harmonization
- Funding & Sustainability
- Regulatory Challenges
- Operations and Implementation

Challenges in Diagnosing Pediatric TB

- Clinical
  - Low sputum production
  - More difficult to diagnose in young, malnourished, and HIV infected children
  - Young age likely have a significant disease burden
  - Acute severe pneumonia
  - MDR TB
  - Extra-pulmonary disease is more common in children
- Microbiologic
  - Pauci-bacillary disease
  - Low sensitivity and low specificity of existing tests
  - Unable to distinguish LTBI vs. TB disease
  - Lack of POC tests
  - Poor timeliness of results

Graham 2014, Cuevas 2014

Epidemiologic Challenges

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*

- 32,000 children with MDR TB in 2010
- Nearly 1 million children with TB disease in 2010
- Risk of MDR TB same in children as in adults reflecting transmission of MDR TB strains
- Many cases of MDR TB and TB are not reported in children

Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study

Dr Peter J Dodd PhD [a], Elizabeth Gardiner MSc [b], Renia Coghlan MPH [c], James A Seddon PhD [d]

- 53M children with latent infection at the end of 2010 (based on cumulative exposure)
- 651,000 (424 871—983 118) children with TB disease in 2010
- Only 35% of Pediatric TB cases are reported

Jenkin 2014, Dodd 2014

Optimal Pediatric TB Diagnostics

- Optimal POC test would be:
  - Affordable
  - Patient-friendly and user-friendly
  - Accurate in people with any form of TB
  - Result in treatment decisions in one visit

- A rapid biomarker-based instrument-free test for non-sputum samples
- A rapid sputum-based molecular test for microscopy centers

Assessment of the novel T-cell activation marker–tuberculosis assay for diagnosis of active tuberculosis in children: a prospective proof-of-concept study

Damien Portevin PhD [a b], Felicien Moukambi MSc [c d], Petra Clowes MD [c d], Asli Bauer PhD [c d], Mkunde Chachage PhD [c], Nyanda E Ntinginya MD [c], Elirehema Mfinanga MD [f], Khadija Said MD [f], Frederick Haraka MD [f], Andrea Rachow MD [d e], Elmar Saathoff PhD [d e], Maximilian Mpina MSc [f], Levan Jugheli PhD [a b f], Fred Lwilla PhD [f], Prof Ben J Marais FCPaed [g], Prof Michael Hoelscher FRCP [d e], Prof Claudia Daubenberger DVM [a b], Dr Klaus Reither MD [a b f †], Dr Christof Geldmacher PhD [d e †]

- TAM TB: T cell activation marker TB
- Measures CD27 phenotype of CD4 T cells producing IFN gamma in response to TB antigens
- Sputum independent blood test providing results within 1 day of blood collection
- Conducted at 2 sites in Tanzania
- Results: 15/18 culture confirmed TB cases were detected
- Sensitivity 83.3% (95% CI 58.6-96.4%)
- Specificity 96.8% (95% CI 89.9-99.6%)

ORIGINAL ARTICLE

Diagnosis of Childhood Tuberculosis and Host RNA Expression in Africa

Suzanne T. Anderson, Ph.D., M.R.C.P.C.H., Myrsini Kaforou, M.Phil., Andrew J. Brent, Ph.D., M.R.C.P., Victoria J. Wright, Ph.D., Claire M. Banwell, Ph.D., George Chagaluka, M.B., B.S., Amelia C. Crampin, F.F.P.H.M., Hazel M. Dockrell, Ph.D., Neil French, F.R.C.P., Ph.D., Melissa S. Hamilton, Ph.D., Martin L. Hibberd, Ph.D., Florian Kern, M.D., Paul R. Langford, Ph.D., F.S.B., Ling Ling, M.B., B.S., Rachel Mlotha, F.C.P. (Paeds) (SA), Tom H.M. Ottenhoff, M.D., Ph.D., Sandy Pienaar, M.Sc., Vashini Pillay, M.B., Ch.B., J. Anthony G. Scott, F.R.C.P., Hemed Twahir, M.Med., Robert J. Wilkinson, F.R.C.P., Ph.D., Lachlan J. Coin, Ph.D., Robert S. Heyderman, F.R.C.P., Ph.D., Michael Levin, Ph.D., and Brian Eley, F.C.P. (Paeds) (SA), for the ILULU Consortium and KIDS TB Study Group*

- TB disease distinguished from other diseases and from LTBI by genome wide analysis of host RNA expression in blood
- Conducted at sites in Malawi, South Africa (discovery cohort), and Kenya (validation cohort)
- 51 transcript signature distinguished TB vs. other disease; 42 transcript signature distinguished TB disease vs. LTBI
- Signatures translated into a single risk score for use in resource poor settings
- Results: Risk score (based on RNA signature) identified culture confirmed TB vs. other disease
  - Sensitivity 82.9% (95% CI 68.6-94.3%)
  - Specificity 83.6% (95% CI 74.6-92.7%)

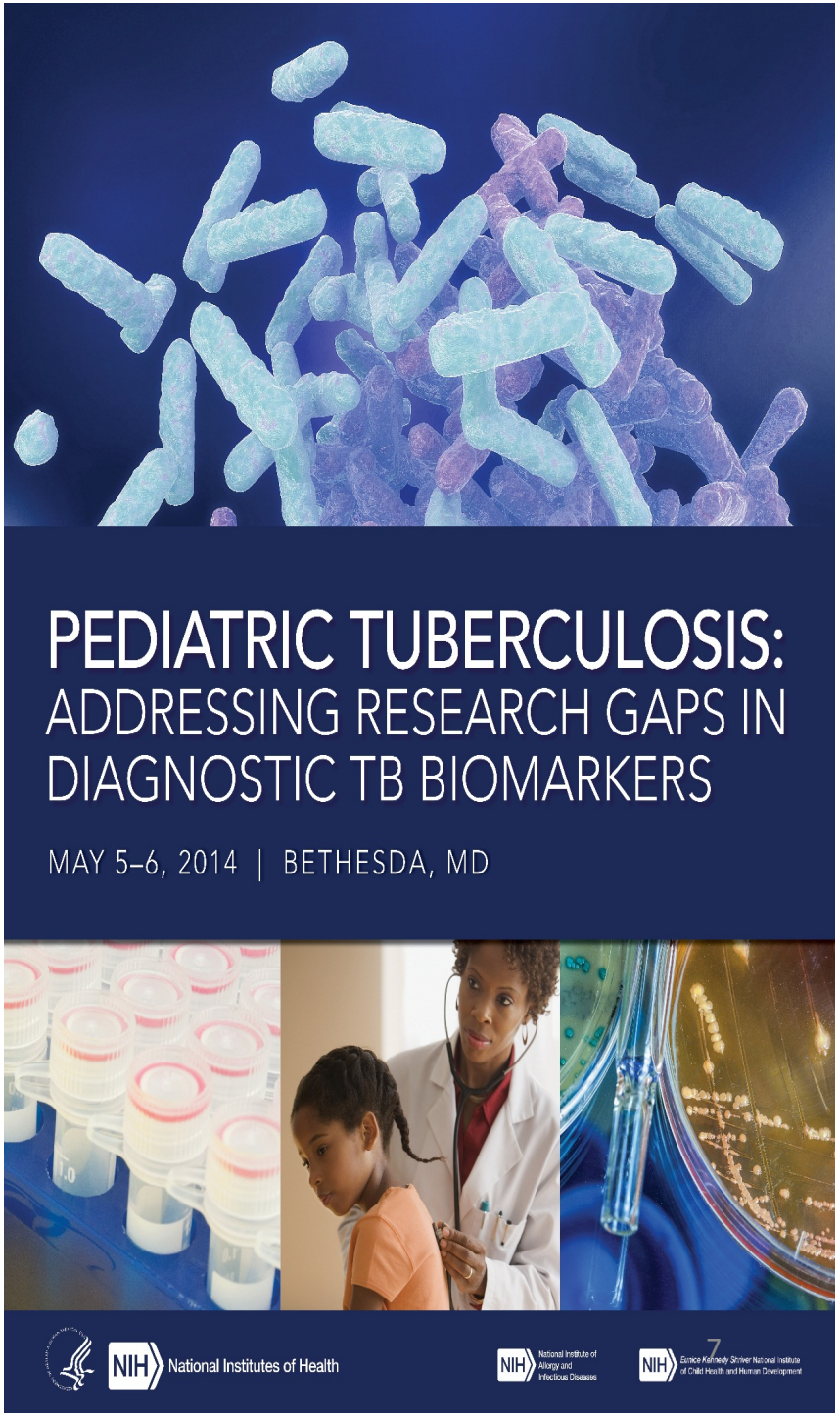
Portevin 2014, Anderson 2014

Attendees (50+)

- University/ Academia
- Non-profit
- US Government
- PIs with ongoing TB repositories
- Chaired by Mark Nicol and Gerhard Walzl

<u>Goals:</u>

- Facilitate diagnosing TB in children through promoting biomarker research
- Define key scientific and operational research gaps and needs
- Promote collaboration among stakeholders and interested organizations
- Pursue harmonized research and development of pediatric TB diagnostic biomarkers
- Coordinate and streamline the long and challenging process to validated and qualified diagnostic biomarkers



Defining priority Pediatric TB biomarker research question(s)

- Identify a new biomarker(s) for diagnosis of TB disease in children who are symptomatic
  - Biomarker for treatment response secondary
- Prioritized study population:
  - Children between 0-5 yrs
    - » Group in which there is greatest difficulty in confirming Dx
    - » Large burden of TB disease
    - » Most severe disease, highest mortality
  - Secondary priority to include children aged 0 - 15yrs
  - Include HIV-infected children
  - Include symptomatic disease for pulmonary and extrapulmonary TB
- Prioritize prospective cohort design that includes adequate follow up

Designing the Repository

- Three options, none mutually exclusive:
  - Development of a de novo, collaborative, federally-funded, globally accessible, centralized biorepository
  - Expansion of existing adult TB repositories, already with vetted approaches, to include pediatric populations
  - **Establish a biorepository consortium/network - A Pediatric TB Shared Biorepository Resource**
- Continue raise awareness/educate major funding agencies on the importance of establishing pediatric TB repositories

Pediatric TB Diagnostic Biomarker Consortium

- Maximize leverage of existing cohorts and biorepositories
  - Pool existing repositories globally
- Establish governance framework
  - Define missions, goals, and development pipeline
  - Oversight and maintenance of the agreed upon principles of ownership, collection, storage, distribution and use of samples.
- Encourage sharing of information and SOPs across investigators
  - Objective to maximize harmonization prior to implementation of studies
  - Minor differences in SOPs should be acceptable
- Develop roadmap
- Include external consultants to advise/guide on the repository formation.
- Regular ongoing meetings

Sample/ Specimen Collection

- Lab working group to create harmonization of methodology across research units and sites
- Develop standardized SOPs
  - Prioritization of specimen types
    - Blood is a priority specimen but need adherence to stringent blood volume collection guidelines for pediatric research
    - Respiratory specimens: remain important due to ongoing biomarker research activities on sputum samples among adults
- Ideal specimen volume, number of aliquots, volume of aliquots
  - Insufficient sample volume is the norm with difficulties in aliquoting; needs to look at having multiple repositories.

Data Harmonization

- Need for a data sharing framework (database interoperability)
- Revisit standard definitions in Pediatric TB
- Reach consensus on required metadata
- Reach consensus on characterization of cohort (mycobacterial evaluation, # of cultures)
- Obtain endorsements (WHO, etc., if possible).

Funding and Sustainability

- Limited interest by major funding agencies due to challenges
  - Substantial investments to build cohort and infrastructure
  - Pediatric funding requirements can be up to 10 times higher compared to adult studies
  - No dedicated funding source for banking so research groups bearing funding
  - Sustainability of repositories questioned leading to even less funding interest
- Involve industry partners early & continue to target major funding agencies
- Consider mandating banking in expensive cohort studies
  - Stipulate/ include certain funding level for biobanking in RFAs
- Consider training/education (e.g. IRBs etc.)
- Establish cost recovery mechanisms
  - Consider different levels based on funding needs, available funds, scientific promise of proposed studies

Regulatory issues and custodianship

- Catalog general principles around biobanking and shipping abroad
  - Develop based on international PI experiences at existing pediatric research sites
- Access: develop clear, flexible, transparent, amenable “Guidelines for Access” for specimens and participant clinical data sharing
- Establish responsibility to curate/maintain these repositories (the individual investigators and specified repositories within networks)
- Specific regulations may vary by country/by sample/by target patient population
  - Consider IP issues and future use consent early
  - Exporting samples may be easier with element of capacity building
- Maintenance of participant confidentiality and de-identification

Operations and Implementation

- Link to mandated tiered pricing of any tools developed such that they are affordable in low and middle income countries
- Include cost recovery mechanisms for the biobank
- Consider implementation of the proposed diagnostic test
- Location of the patient and the diagnostic platform
- Time required for…
  - Sample to reach the lab
  - Results to reach the patient
  - Clinician to meet the child
- Perception of the test
- Anticipating bottlenecks and planning to avoid these