Childhood Tuberculosis

Launch of the Centre for International Child Health
29th January 2016

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Imperial College London
Introduction

• Paediatric tuberculosis fascinating topic
• Quite a challenging field to work in
• Exciting times
  • More funding
  • More research
  • More interest
• Opportunity
  • Advance field
  • Make a significant difference to some of the most vulnerable and marginalised children
Why is paediatric tuberculosis important?

Donald PR. Curr Opin Pulm Med 2002
Tuberculosis

- Immunology
- Epidemiology
- Diagnostics
- Vaccinology
- Treatment
Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris*, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane‡, and the MVA85A 020 Trial Study Team

Making a diagnosis

Child with symptoms

Identification of host response to organism

Identification of organism

Phenotypic identification of organism

Phenotypic identification or resistance

Genotypic identification of organism

Genotypic identification of resistance
The impact of Bacillus Calmette–Guérin vaccination on tuberculin skin test responses in children is age-dependent: evidence to be considered when screening children for tuberculosis infection.

NIKS study team. Thorax. Under review
Diagnosis of Childhood Tuberculosis and Host RNA Expression in Africa

Making a diagnosis

Child with symptoms

Identification of host response to organism

Identification of organism

Phenotypic identification of organism

Genotypic identification of organism

Phenotypic identification or resistance

Genotypic identification of resistance
Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

1. Sputum liquefaction and inactivation with 2:1 sample reagent
2. Transfer of 2 ml material into test cartridge
3. Cartridge inserted into MTB-RIF test platform (end of hands-on work)
4. Sample automatically filtered and washed
5. Ultrasonic lysis of filtrate-captured organisms to release DNA
6. DNA molecules mixed with dry PCR reagents
7. Semi-nested real-time amplification and detection in integrated reaction tube
8. Portable test result

Time to result, 1 hour 45 minutes

Smear status
- Smear positive
- Smear negative

Culture
- Culture positive
- Culture negative

Xpert MTB/RIF
- GeneXpert positive
- GeneXpert negative
Why understanding the epidemiology important?

• Who, where, when
• Targeting resources
• Discrepancies
• Sentinel event
• Market assessment
• Advocacy
Challenges

- Few cases confirmed
  - Difficult to obtain specimens
  - Paucibacillary disease
  - Limited laboratory capability
  - Greatest challenge in youngest children
- Under-reporting
  - Previously only sputum smear-positive cases reported
  - Private sector frequently not reported
Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study

Peter J Dodd, Elizabeth Gardiner, Renia Coghlan, James A Seddon
Burden of drug-resistant tuberculosis

<table>
<thead>
<tr>
<th>DST</th>
<th>S</th>
<th>INH</th>
<th>RIF</th>
<th>MDR</th>
<th>FQR</th>
<th>SLR</th>
<th>XDR</th>
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</thead>
<tbody>
<tr>
<td>Disease</td>
<td>753,096</td>
<td>40,289</td>
<td>6,156</td>
<td>18,603</td>
<td>2,566</td>
<td>2,731</td>
<td>1,988</td>
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<tr>
<td>Infection</td>
<td>57,305,870</td>
<td>3,088,543</td>
<td>452,635</td>
<td>1,413,608</td>
<td>201,005</td>
<td>228,580</td>
<td>167,223</td>
</tr>
</tbody>
</table>

DST, S, INH, RIF, MDR, FQR, SLR, XDR columns represent disease and infection counts.

Dodd et al. In prep
Relationship between HIV and tuberculosis in children

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>HIV in TB (n/N)</th>
<th>HIV in controls (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berggren Palme, 2001</td>
<td>47 / 377</td>
<td>2 / 122</td>
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<tr>
<td>Bhat, 1993</td>
<td>36 / 96</td>
<td>18 / 134</td>
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<tr>
<td>Chintu, 1993</td>
<td>86 / 237</td>
<td>26 / 242</td>
</tr>
<tr>
<td>Chintu, 1995</td>
<td>42 / 61</td>
<td>15 / 160</td>
</tr>
<tr>
<td>Luo, 1994</td>
<td>67 / 110</td>
<td>16 / 167</td>
</tr>
<tr>
<td>Mukadd, 1997</td>
<td>31 / 160</td>
<td>0 / 161</td>
</tr>
<tr>
<td>Rose, 2012</td>
<td>18 / 33</td>
<td>22 / 93</td>
</tr>
<tr>
<td>Yassin, 2011</td>
<td>14 / 141</td>
<td>3 / 153</td>
</tr>
</tbody>
</table>

RE summary OR [95% CI]: 7.9 [4.5–13.7]

First author, Year
- Auld, 2014
- Bakarea-Kitaka, 2011
- Braitsstein, 2009
- Brennan, 2014
- Crook, 2016
- Curtis, 2012
- De Beaudrap, 2013
- Edmonds, 2009
- Liu, 2013
- Walters, 2014

Odds Ratio (log scale)
Mortality in children due to tuberculosis

On tx (HIV-)
Off tx (HIV-)
On tx (HIV+)
Off tx (HIV+)

Deaths in children due to TB

WPR
SEA
EUR
EMR
AMR
AFR

0 to 524
524 to 1,978
1,978 to 6,080
6,080 to 18,080
18,080 to 42,332
No data

Dodd et al. In prep
Treatment of MDR-TB disease

Treatment of MDR-TB infection

Treatment of DS-TB disease

Treatment of DR-TB infection

Treatment of TB Meningitis

New Drugs
PAEDIATRIC MDR-TB

Individual Patient Data Meta-Analysis

Anneke Hesseling, Simon Schaaf, Tony Garcia-Prats, Jennifer Furin & James Seddon

as part of the

Desmond Tutu TB Centre; Stellenbosch University; Cape Town, South Africa

are seeking collaborators for a

Evidence synthesis to inform the paediatric component of revised WHO guidelines on the management of multidrug-resistant tuberculosis

If you have individual patient data regarding treatment outcomes for paediatric MDR-TB and are interested in collaborating on this very exciting project, for more information please contact:

Elizabeth Harausz at epharusz@gmail.com
Children < 5 years
(aged 1-5 years TST positive or < 12 months regardless of TST)
with known MDR-TB adult contact in the household
N=988 households

Randomise
(1:1)

INTERVENTION ARM
Treatment Phase:
6 months daily dosing of levofloxacin
Follow-up phase:
18 months post-treatment

CONTROL ARM
Treatment Phase:
6 months daily dosing of placebo
Follow-up phase:
18 months post-treatment
SURE
ERS/WHO Tuberculosis Consilium assistance with extensively drug-resistant tuberculosis management in a child: case study of compassionate delamanid use
Tuberculosis

- Epidemiology
- Diagnostics
- Immunology
- Vaccinology
- Treatment
Conclusions

• Childhood TB big problem globally
• Important problem in the UK
• After a long period of little investigation lots of work now being done on paediatric TB
• Lots being done at Imperial
Questions?