Childhood Tuberculosis – Some Basic Issues

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TUBERCULOSIS IS A SOCIAL DISEASE WITH MEDICAL IMPLICATIONS

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LAKES

THE GREAT PARADOX OF TUBERCULOSIS – A CAUTIONARY TALE

By the use of drugs and BCG vaccines, we can

- **cure tuberculosis disease [for less than 75 US dollars]**
- **prevent progression of tuberculosis infection into disease**
- **prevent a significant proportion of life-threatening childhood tuberculosis [by BCG vaccination]**

Yet, tuberculosis remains one of the three greatest infectious disease menaces for humans, and our inability to control it is our biggest public health failure.

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EPIDEMIOLOGY OF CHILDHOOD TUBERCULOSIS IN SELECTED HIGH-BURDEN COUNTRIES

Country	Childhood Cases	% Total Cases	Case Rate Children	Case Rate Total
Afghanistan	17.540	25.3	189	324
Brazil	23,520	20.7	47	66
China	86,978	5.3	27	129
Pakistan	61,905	25.3	103	172
South Africa	35,449	16.1	237	501
Zimbabwe	12,267	16.1	221	603
Range		2.7-25.3	15-237	66-603
Total	659,397	9.6		

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BURDEN OF CHILDHOOD TUBERCULOSIS IN DEVELOPING COUNTRIES

- 40% of cases may be in children
- May account for up to 10% of children's hospital admissions
- May account for 10% or more of hospital deaths in children
- Annual rate of infection up to 3% or higher in children in many countries

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ECONOMIC AND SOCIAL BURDEN OF TUBERCULOSIS FOR CHILDREN

- Direct treatment costs
- Inpatient or institutional treatment
- Transportation costs for care
- Lost earnings of the family
- Redirecting resources from other needs
- Withdrawal from school
- Creation of orphans [parents with TB/HIV]
- Stigmatization and discrimination

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Should Primary Tuberculosis in Children Continue to be Neglected?

KHK Hsu *J Pediatrics* 1956; 48: 501

"Primary tuberculosis is the fountainhead of tuberculous diseases. When acquired during childhood, it may develop into serious tuberculous diseases within a short period of time, or remain latent during childhood, only to be become reactivated in adult life."

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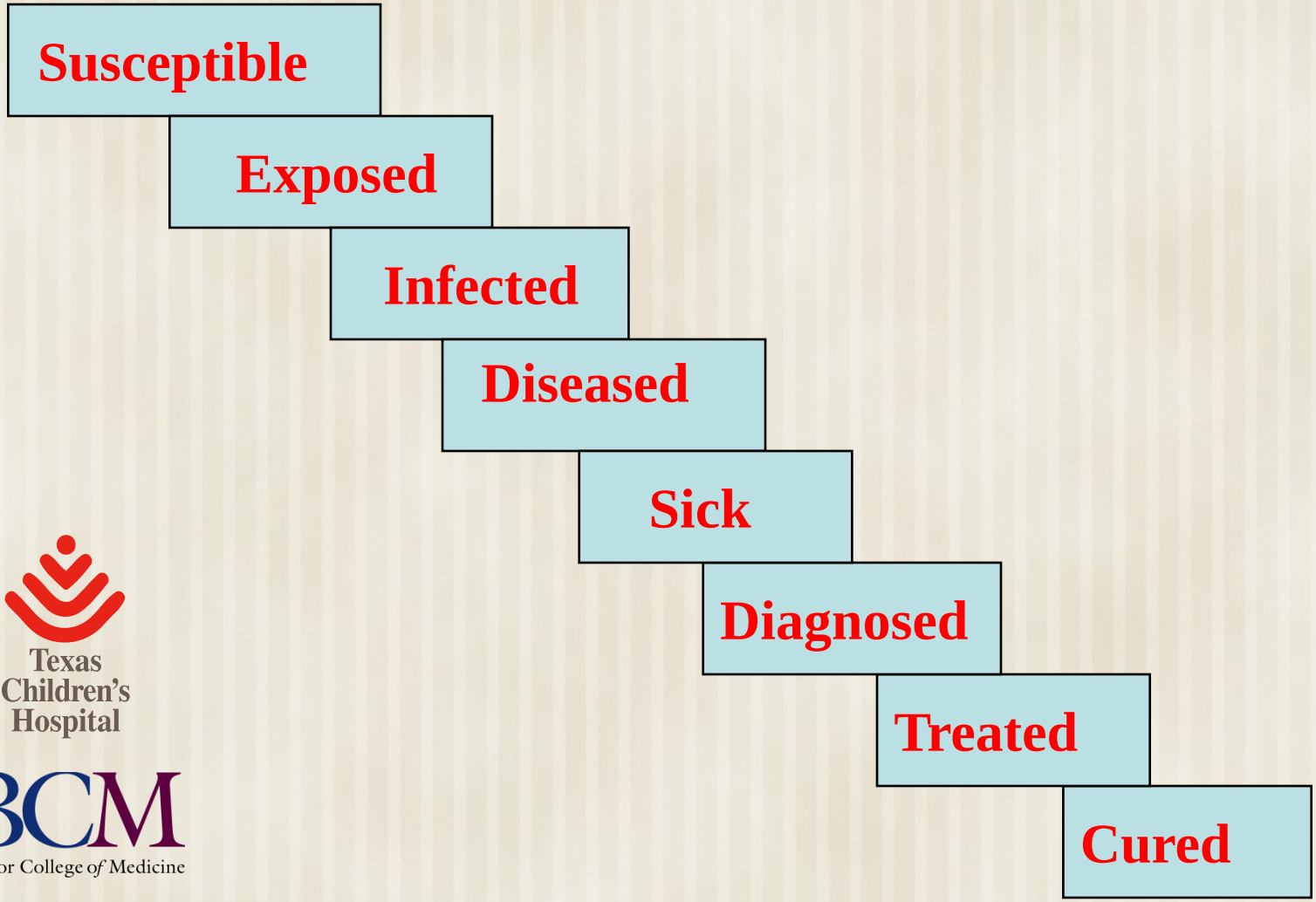
TRANSITIONS IN TUBERCULOSIS



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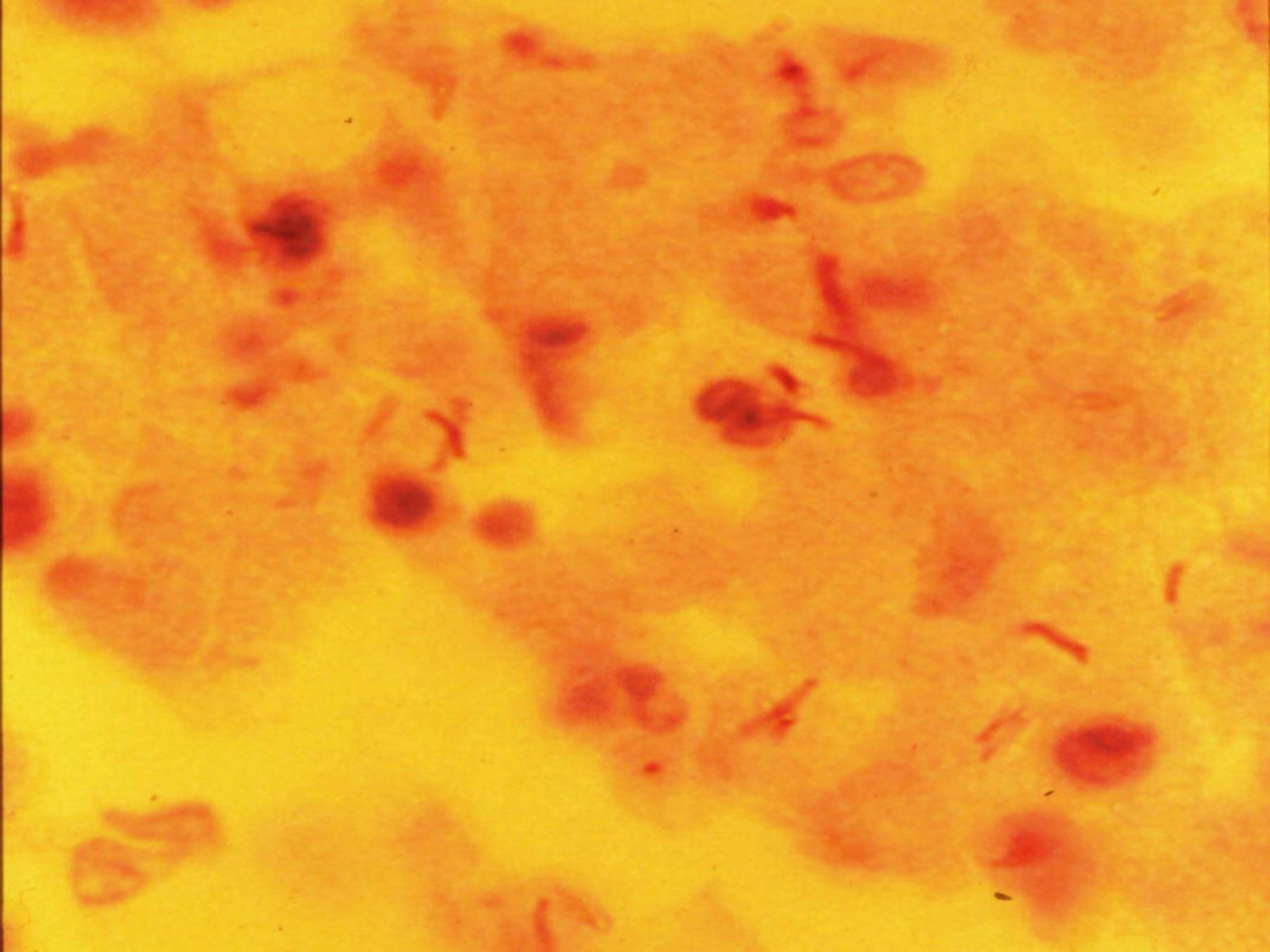
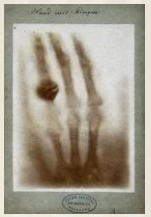
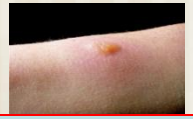
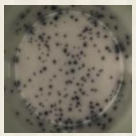


Tuberculosis: A Low Tech Disease Even In 2012

- ~ 400 BC: Hippocrates [H&P] 
- 1882: Koch [TB culture] 
- 1895: Rontgen [x-ray] 
- 1907: Mantoux [TST] 
- 1983: Mullis [PCR] 
- Late 1990's: IGRAs 

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HOW IS TUBERCULOSIS DIAGNOSED?

Adults – Mycobacterial-based diagnosis

- positive sputum AFB smear - 60% - 75%
- positive sputum culture - 90%
- positive tuberculin skin test - 80% [HIV < 50%]

Children

- positive sputum or gastric AFB smear - 10%
- positive sputum or gastric culture - 10% - 40%
- positive tuberculin skin test - 50% - 80%

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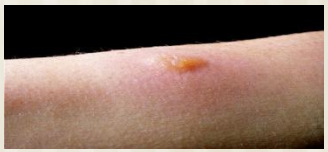
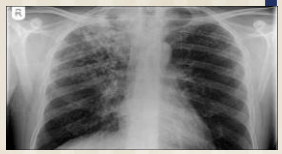
DIAGNOSIS OF TUBERCULOSIS

Even in developed countries, the "gold standard" for the diagnosis of tuberculosis in children is the triad of:



1. a positive TST
2. an abnormal CXR and/or physical exam



3. a history of recent contact to an infectious adult case of TB

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ADVERSE EFFECTS IN CHILDREN OF NOT PERFORMING CONTACT TRACING

- Missed cases
- Misdiagnosis – tuberculosis not recognized
- Diagnose cases later – increased morbidity and mortality
- Missed drug resistance [need source case culture and drug susceptibility results]
- Missed prevention – treating exposed or infected children

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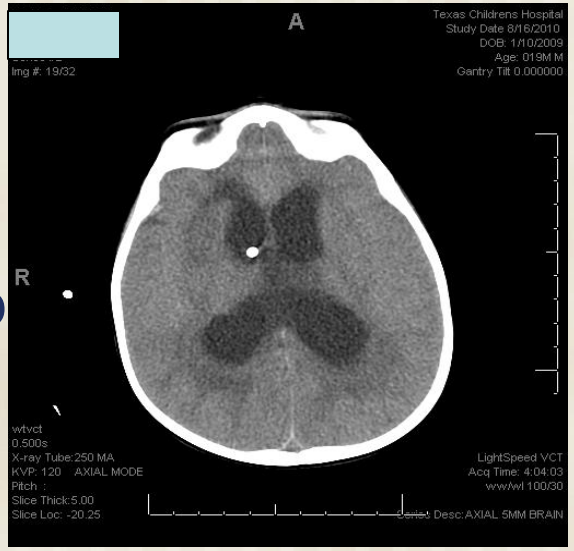
A Difficult Case

A 19 mo old child in Houston presents acutely to an OSH with a several day history of fever, agitation and lethargy, and a possible generalized seizure.

An emergent EVD is placed, he is transferred to TCH. CXR is WNL, no family hx of TB. He is started on broad spectrum antibiotics



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A Difficult Case

- CSF taken directly from the brain was normal
- CSF taken from the spine was very abnormal, indicating meningitis
- All cultures for tuberculosis were negative
- The tuberculin skin test yielded 0 mm of induration, and the QuantiFERON was indeterminate
- The T.Spot *TB* IGRA was "wicked positive"
- 3 weeks later, the mother's boyfriend's sister [child's babysitter] was found to have pulmonary TB
- The child had a typical course for TB meningitis and improved slowly on anti-TB medications

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TB Studies on Adults & Children

Modality	Adult Studies *	Pedi Studies *	Δ	Ratio adult to pedi	Year of 1st publication
Culture: Solid	400	38	-362	11x	1967
Culture: Liquid	248	13	-235	19x	1966
MODS	37	7	-30	5x	2000
PPD/TST	6399	2031	-4368	3x	1907
IGRA	344	87	-257	4x	1999
Xpert	7	1	-6	7x	2010
PCR, all	1831	187	-1644	10x	1990

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*: PubMed Queries

New TB Tests Are Not Applied to Children

Test	# of published studies in children
FNA	140
Fluorescent microscopy	1
LED-FM	0
MODS	3
Line-probe assays	1
LAMP	0
GeneXpert	1

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A Fundamental Question

Much of the attention for HIV and malaria has focused on children, but this has not happened for tuberculosis:

Why not?

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SOME REASONS WHY CHILDHOOD TUBERCULOSIS HAS BEEN NEGLECTED

- Difficulty confirming the diagnosis
- Children are rarely contagious
  [public health “dead end”]
- Perception from TB policy makers that treating adults is enough
- Government programs fail to address children
- Lack of family centered contact tracing
- Perceived lack of scientific study and scrutiny
- Misplaced faith in the BCG vaccines
- Lack of industry support
- Inadequate advocacy by pediatricians

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The Good News

- Improved advocacy on the international level has increased attention on children and TB
- Increased research capacity is being developed in high burden countries
- Better organization by pediatric TB experts
- Recent international meetings in Stockholm and by the NIH have fostered enthusiasm and collaboration
- Inclusion of children in major research efforts

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Ten Truths About Childhood Tuberculosis

1. Much childhood tuberculosis is preventable with simple, inexpensive measures.
2. Non-preventable childhood pulmonary tuberculosis can be found earlier when it is easier to treat.
3. Finding and treating adults with tuberculosis is not sufficient for controlling childhood TB.
4. BCG vaccines alone cannot control childhood tuberculosis.
5. Infection control has been largely neglected in high burden areas.

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Ten Truths About Childhood Tuberculosis

6. Chest x-ray is essential to diagnose pulmonary tuberculosis in children.
7. Adequate tuberculosis control for children requires a robust public health system with contact tracing and interagency cooperation.
8. Children with tuberculosis infection are a huge reservoir for future adult tuberculosis cases.
9. Childhood tuberculosis really is a window into the overall effectiveness of tuberculosis control.
10. Additional basic and translational research into childhood tuberculosis are badly needed.

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What Is Needed For Childhood Tuberculosis

- Improved diagnostic tests
- Pediatric dosage forms of new and old drugs
- Early inclusion of children in studies of new drugs and diagnostics
- Funding for translational research
- Improved health care systems
- A better vaccine

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CHILDHOOD TUBERCULOSIS: THE HIDDEN EPIDEMIC

Donald Int J Tuberc Lung Dis 2004; 8:627

"The time has come for the hidden epidemic of childhood tuberculosis to emerge from the shadow of adult tuberculosis and be seen as a neglected child health problem of considerable proportions in precisely those communities that do not have the resources to deal with it adequately."

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