Diagnosis of tuberculosis in children

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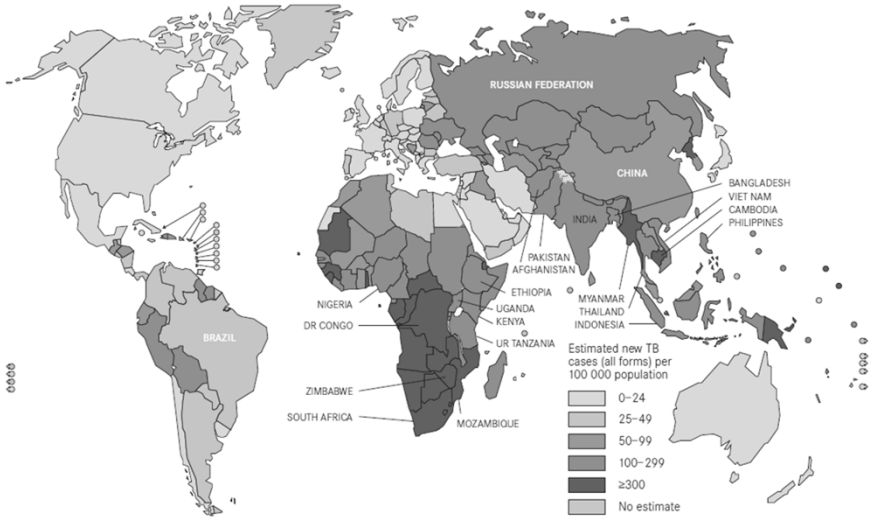
Estimated TB incidence rates 2010



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Epidemiology

~500 000 new TB cases in South Africa/year (1% of population)

Children make up 15-20% of the national TB burden

Surveillance of drug resistance in adults last done in 2001, but WHO estimates 13 000 new MDR-TB cases/yr in SA, of which also ~15-20% will be in children

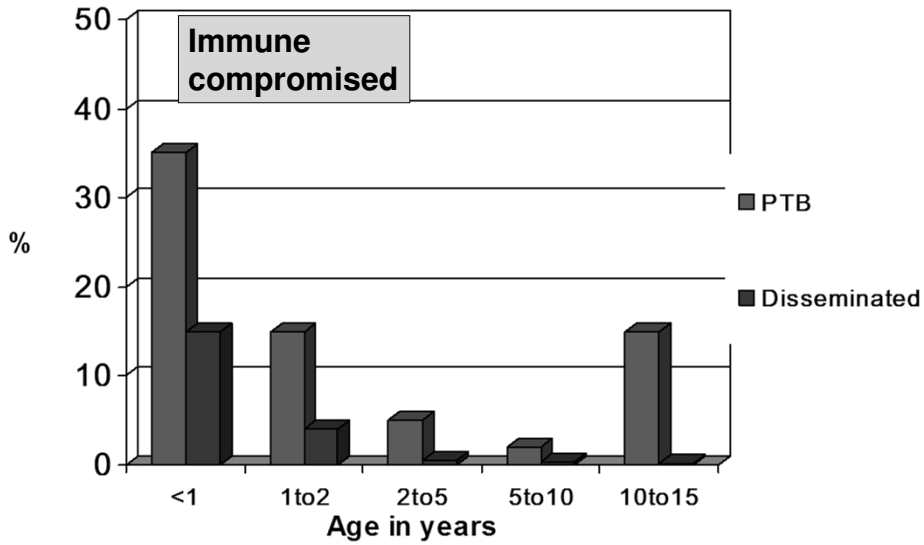
Of concern is a rising trend also of RIF-monoresistant TB

Conventional approach to TB diagnosis

A constellation of the following:

- History of chronic symptoms and TB contact
- Clinical examination (incl. growth assessment)
- Tuberculin skin testing (or IGRAs?)
- Chest radiography
- Bacteriological confirmation
- Histology (especially EPTB)
- HIV testing (high prevalence areas or patients at risk)
- (Scoring systems and diagnostic algorithms)

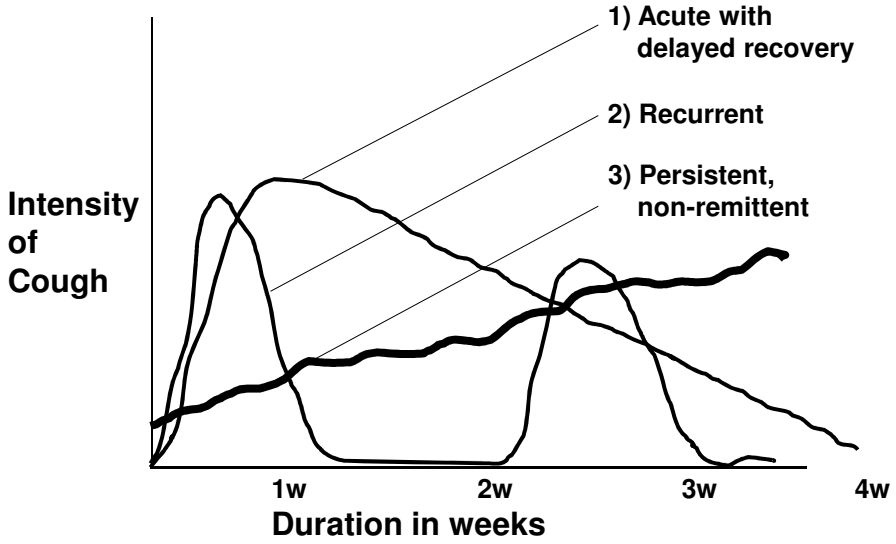
Age-related risk



History of symptoms of chronic disease

- Symptoms may overlap with other diseases, but well-defined symptoms give improved yield:
  - Chronic cough = unremitting cough >3 weeks
  - Fever = >7-14 days after excluding common causes
  - Weight loss or FTT = preferably documented on growth chart (RTHC)
  - Fatigue (tiredness) – not keeping up with others
- In some children TB presents as an acute pneumonia; both in HIV-infected and -uninfected

Symptom characteristics



History of contact

- A close contact = living in the same household (or in frequent contact) with source case.
- Sputum smear-positive TB case > infectious than smear-negative source cases, but still infectious!
- Screen all children (especially <5 years or HIV-infected) in HH contact with PTB cases for TB
- Contact with source case is found in only 40-70% of cases. May be infected outside of household
- Often undiagnosed or other TB cases in the family - in infants, may be worthwhile to screen mother
- Find out about DST of adult source cases!

Clinical examination

- There are no specific features on clinical examination to confirm that presenting illness is due to pulmonary TB

- Physical signs highly suggestive of EPTB:
  - Gibbus, especially recent onset (spinal TB)
  - Non-painful cervical lymphadenopathy with fistula formation

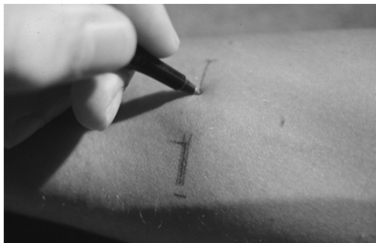
Clinical examination

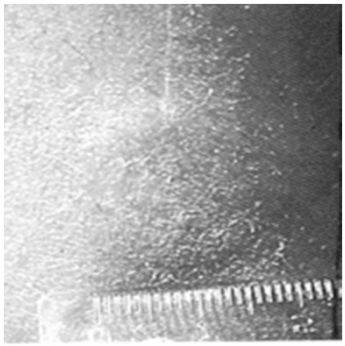
Physical signs requiring investigation for EPTB:

- Meningitis: with sub-acute onset or not responding to AB
- Pleural effusion – older children
- Pericardial effusion
- Distended abdomen with ascites
- Non-painful cervical lymphadenopathy without fistula formation
- Signs of tuberculin hypersensitivity (phlyctenular conjunctivitis, erythema nodosum, PNT)
- Painful joint(s)

Tuberculin skin test (TST)

- Useful to identify children infected with TB
- Mantoux TST the recommended test
- Read in mm induration after 48-72 hours. Regarded as positive as follows:
  - High-risk children: ≥5 mm (HIV-infected or severely malnourished children)
  - All other children: ≥10 mm
- Negative TST does not rule out TB





Interferon-gamma release assays

- Based on release of IFN-γ produced by T-cells
- Two blood tests commercially available
  - T-Spot.TB (ELISPOT)
  - Quantiferon-TB Gold In-tube test
- Diagnose infection and not disease (as TST)
- More specific than TST – not affected by BCG
- IGRAs possibly more sensitive than TST, but this has not been confirmed in high-burden areas
- Time to lab / amount of blood / cost – are limitations
- May be specific indications for use, but many studies still evaluating its role in children

Chest Radiography

Remains an important tool in diagnosis although:

- Quality of radiographs are important
- Chest radiographs often misread in children with TB. Intra- and inter-observer error for hilar lymphadenopathy common

Suggestive pictures

- Enlarged hilar and/or mediastinal lymph nodes with or without (persistent) opacification in the lung
- Ghon focus/complex (uncommon)
- Miliary pattern in HIV-uninfected children
- Adolescents: adult type PTB or pleural effusion

HIV/TB: Chest Radiography

Basic features the same. Often more difficult to interpret:

- HIV-associated lung conditions look similar to TB, e.g. bronchiectasis, recurrent pneumonias, LIP
- TB can occur concurrently with other diseases

Reticulonodular (miliary) picture ± adenopathy

- could be miliary TB, LIP or other conditions

Reports: (Madhi IJTLD 2000, Hesseling IJTLD 2002)

- more cavitation in HIV+ TB
- more miliary TB in HIV+ TB

Most children with TB are <u>not</u> HIV-infected!

Other imaging (remember EPTB)

- Ultrasound: Abdominal TB, pleural and pericardial effusions
- CT scans: TBM, chest mainly
- MRI scans: Spinal TB, TBM
- Bronchoscopy: lymph nodes and its effects

HIV-infected *vs*. non-HIV-infected

- There are still many more HIV-uninfected children with TB than HIV-infected
- Treat HIV-infected children as a high-risk group (infection is as important as disease). As immune status deteriorates (lower CD4%), risk for TB increases
- Early HAART will reduce risk between 3-10 times, but risk remains higher than in HIV-uninfected children

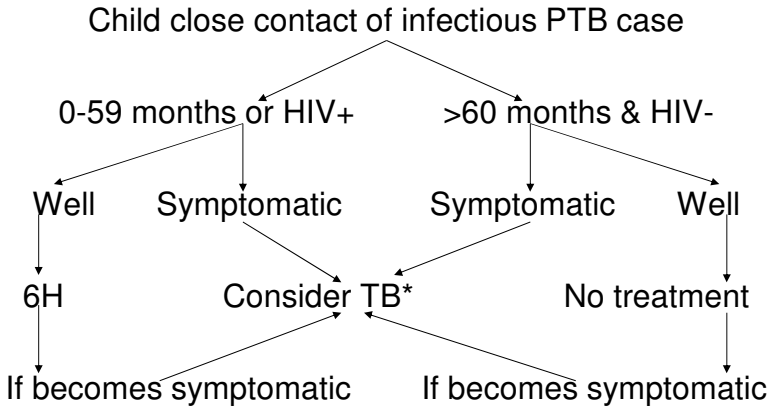
Point Scoring System

Feature	0	1	2	3	4	Score
GENERAL						
Weeks ill	< 2	2 – 4		> 4		
WFA	> 80%	60 – 80%		< 60%		
Family history	None	Reported		Sputum +		
Tuberculin				Positive		
Malnutrition				Not improving		
Fever			No response			
LOCAL						
				Lymph ad.		
				Bone / joint		
				Abd. mass		
				CNS sg / CSF		
					Gibbus	
						TOTAL

Scoring systems or diagnostic approaches

- Critical review of these approaches shows that few have been tested and sensitivity and specificity has not been calculated
  (*A Hesseling et al. IJTLD 2002;6:1038-45)*
- In an area with high HIV prevalence the specifity was 25% (95% CI 16-37%)
  (*P van Rheenen. Trop Med Int Health 2002;7:435-41)*
- In developing countries scoring systems is all that is available – stepwise approach – more a screening tool than a diagnostic tool

Contact management algorithm



***Follow guidelines for diagnosis**

How to investigate contacts

Clinical assessment:

- History (Symptoms; closeness and duration of contact; drug resistance)
- Clinical examination

Clinical assessment alone is sufficient to decide whether contact is well or symptomatic

If available:

- TST (exposure – prophylax even if TST negative)
- CXR (for diagnosis of disease)

Why do we need microbiological confirmation?

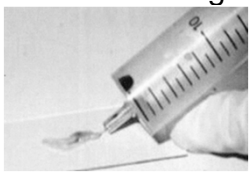
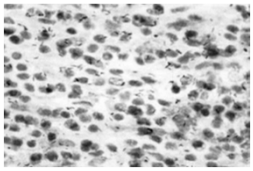
- The majority of child TB cases are diagnosed at primary care level without microbiological confirmation, as specimens from children are difficult to obtain and often those children have primary (paucibacillary) TB
- In >80% of culture-confirmed cases in hospital the diagnosis of TB was made before culture result was available
- If DST of adult source case is known, child contact should be treated according to adult isolate's DST result, as concordance between source case and child's isolates is between 78-90% in different studies

Why do we need microbiological confirmation?

- To confirm TB in difficult cases, e.g. uncertain lung pathology, HIV-infected children, extrapulmonary TB
- To determine drug susceptibility in children with unknown source cases, especially if they have poor response to first-line treatment
- To confirm drug resistance if a source case with DR-TB is identified – in our experience up to 20% not the same DST pattern as source case, either because different source case or infected before amplification of resistance in the source case

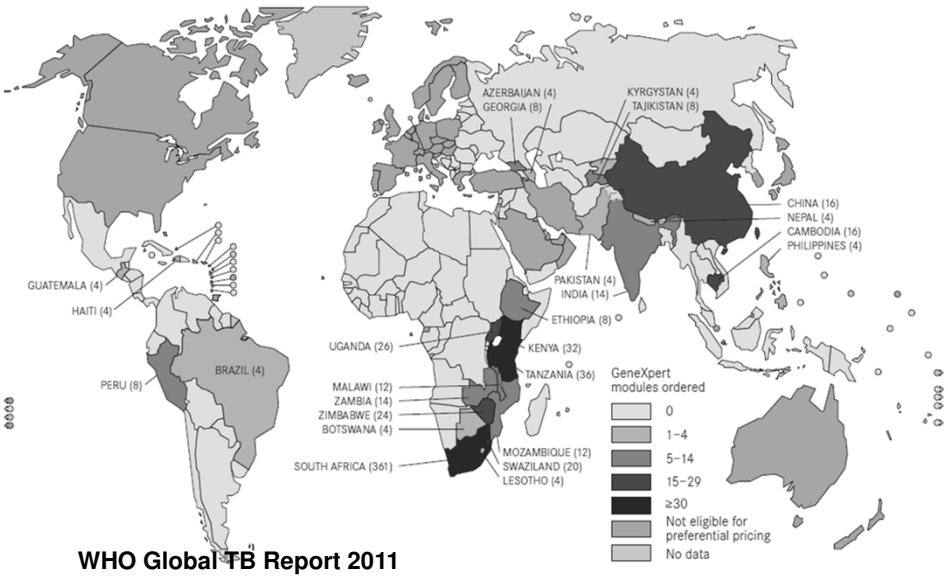
Culture for *M. tuberculosis*

- Only 5-10% smear-positive yield in children
- Cultures positive in 30-40% of hospital-based cases; lower in community-based studies.
- Respiratory samples in children:
  - Induced sputum ~ gastric aspirate
  - NPA, tracheal aspirates or BAL
- FNA biopsies are useful for diagnosis of EPTB

- Any other body fluid/biopsy of tissue suspected of TB (e.g. CSF, bone/sinovial biopsy)

Progress in the role-out of Xpert MTB/RIF, as of June 2011



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GeneXpert MTB/RIF

- GXP – PCR-based diagnosis of both *M.tuberculosis* complex as well as RIF resistance. Becoming more of point-of-care test and replacing sputum smear microscopy, but culture still needs to be done to confirm results and, in case of RIF resistance, to confirm MDR-TB and do second-line DST
- Mainly done on sputum samples, but several studies have shown its value also with other specimens, e.g. GA, FNA from lymph nodes

DST in children

- Culture & DST – takes longer but provides best yield (30-70% in symptomatic children). Phenotypic or genotypic DST can be done, the latter providing more rapid results
- Xpert MTB/RIF should in children be followed by culture and DST, because children usually have smear-negative disease, and only ~60% of smear-neg, culture-pos cases will be identified.
- Xpert MTB/RIF also does not provide further DST results other than RIF (currently mainly sputum used)
- With increasing RIF-monoresistant TB cases in adults and Xpert MTB/RIFresults only, managing child contacts becomes a problem

Line Probe Assays

- Line-probe assays, a family of DNA strip-based tests that use PCR and reverse hybridization methods for the rapid detection of mutations associated with drug resistance, are available as commercial kits.
- Confirms *M. tuberculosis* complex and provides drug susceptibility test (DST) results for INH and RIF
- GenoType MTBDR*plus* – INH and RIF mutations
- GenoType MTBDR*sl* – second-line drugs
- Problems: Need laboratory set-up, risk of cross contamination
- Advantage: identifies the mutation conferring resistance to INH. This could assist with choosing the correct drugs, e.g. high-dose INH vs ethionamide

Conclusion of present data

- There is very little new data that has dramatically changed our ability to diagnose TB in children
- The more proof, the more certain the diagnosis
- Scoring systems, despite its shortcomings may still have a role to play as a screening tool in certain settings
- Younger children are at greater risk for complications e.g. disseminated TB and TBM, therefore treat earlier
- Role of culture/DST – confirming diagnosis and identification & confirmation of drug resistance