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Gaps in the diagnosis and management of severe TB in children

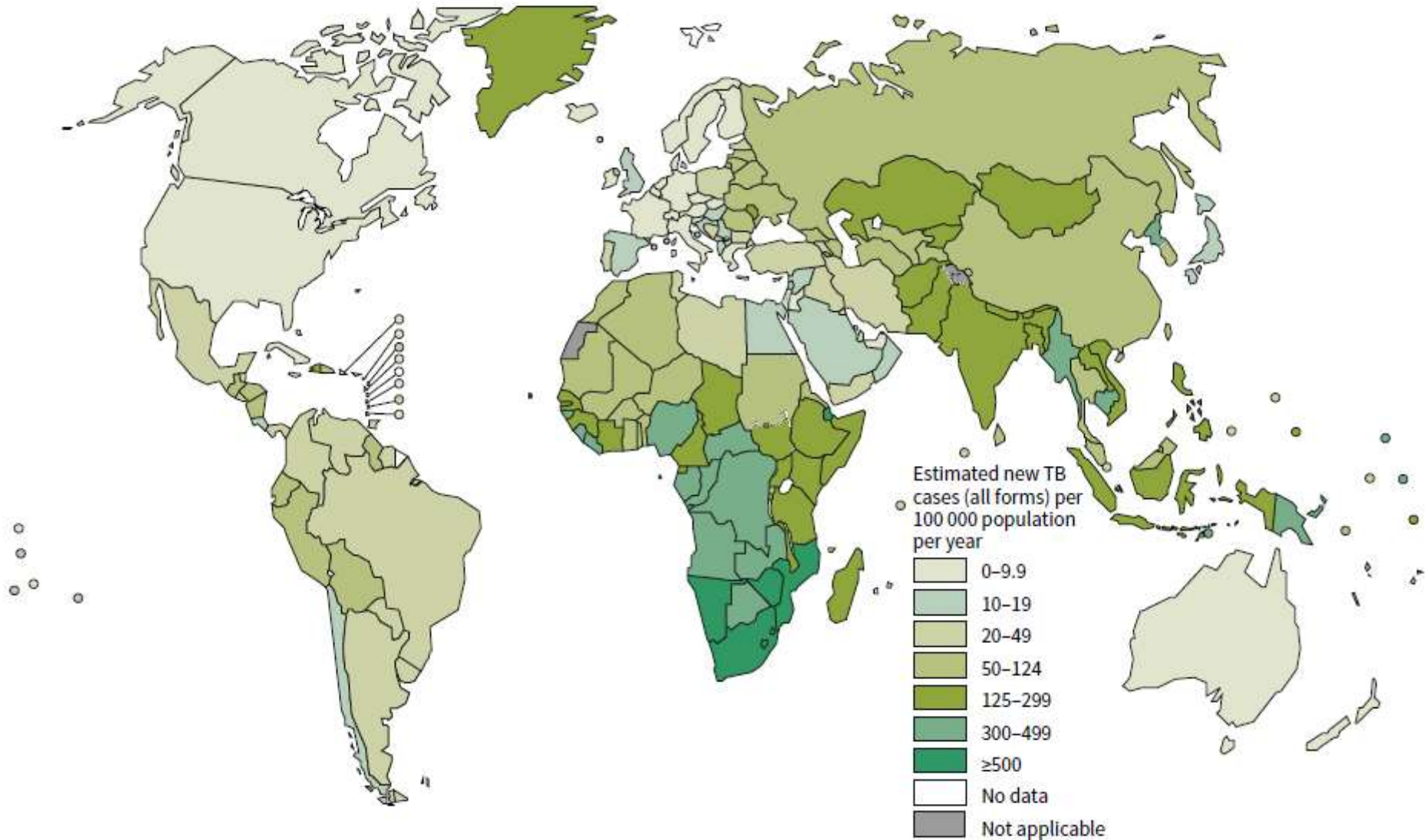
Red Flags

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Estimated TB incidence rates, 2013



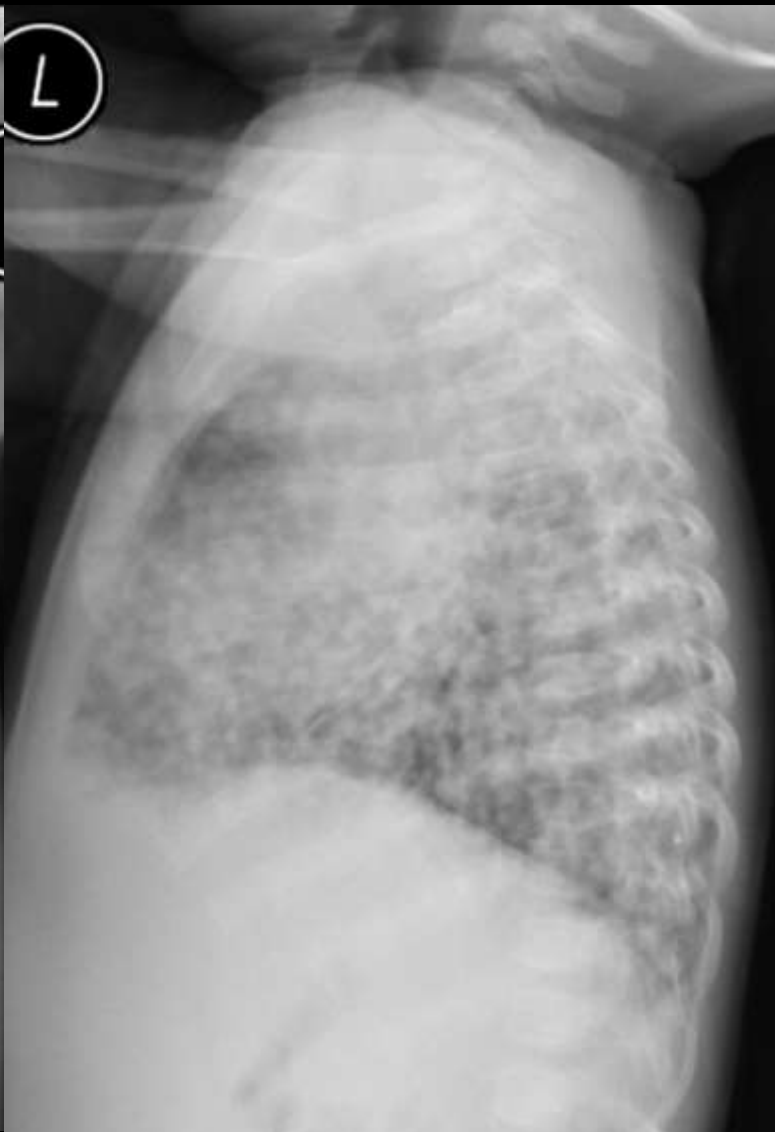
Introduction

- South Africa has the highest incidence of TB cases (860 cases [776-980] per 100 000 population) among the 22 High Burden Countries in the world.
In SA almost 1% of the population gets TB every year!
- 15-20% of South Africa's ~500 000 cases are amongst children.
- In adults 50-70% HIV-infected, but lower in children
- WHO estimated 480 000 new MDR-TB cases worldwide in 2013
- MDR-TB surveillance data in children is poor, but recent estimates vary between 32 000 and 50 000 cases in children
- **We should ALL be very aware of TB in children irrespective of where we work!**



Case 1

- 14-week-old girl – cough >4 weeks (severe coughing spells) and fever 2 weeks
- Was seen at clinic several times. Antibiotics given >1 course. Mom told stop smoking
- No BCG (born at home). Only had 6-week immunisation (to ill?)
- Breastfed since birth, but on clinic card not thriving
- No TB at home – mom had TB 2009
- Mom says she is coughing “on and off” – describes it as a “normal cough”
- O/E: Low grade fever, decreased air entry LUL, HSM
- Irritable baby, no neck stiffness or bulging fontanel, bilateral femoral hernias



Case 1

Results:

- HIV-negative
- Gastric aspirate smear and culture positive – DS-TB
- LP: CSF prot 0.7g/l, glucose 2.8 mmol/L, polymorphs 10, lymphocytes 6, RBCs 2 (Stage 1 TBM)

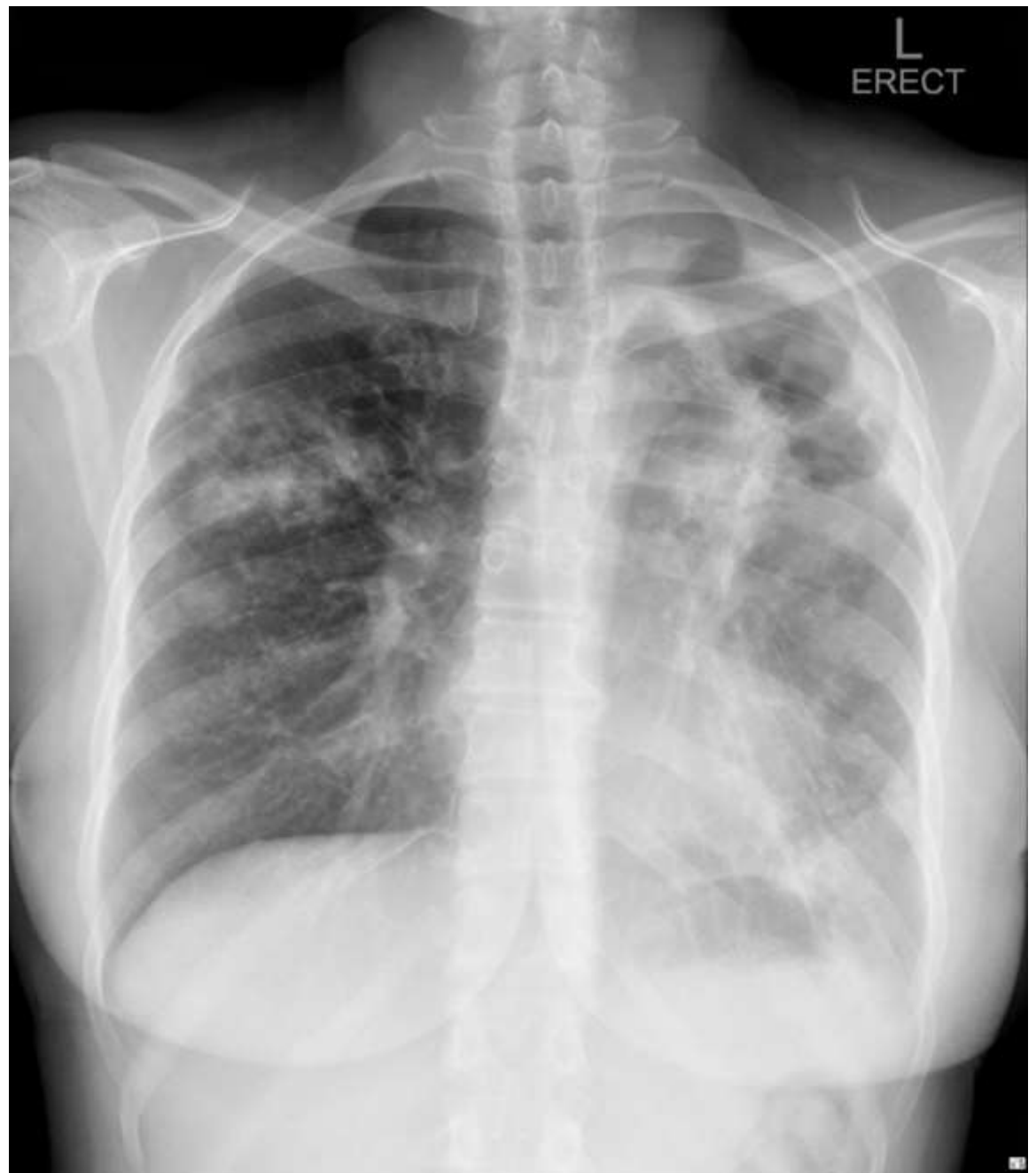


- Young infants DO GET TB – high morbidity (severe forms of TB) and high mortality
- 5-8% of culture-confirmed cases at TBH are <3 months of age

- Mother's CXR who had a "normal cough"
- In infants the caregiver is the most likely source case (often unaware of their own TB)



- **Infectious adults in the clinic/ward!**



Case 2

- 18-month-old girl
- Few days history of vomiting, apathy and 3-month documented LOW
- Presented to hospital with L-sided focal seizures
- Previous history
 - Had few clinic visits/GP visit – antibiotics received for OM, but no improvement
 - Mother HIV-infected defaulting ARVs
 - Mother drug-susceptible TB – defaulted treatment
- No INH preventive therapy or previous HIV testing
- Had BCG at birth, 18-month immunisations due

Case 2

- On examination:
Weight 8.2 kg = -2 Z-score WfA
GCS 12/15, 3rd Cranial nerve palsy, oral thrush and generalised LAD. Hepar 5cm below costal margin
- Special investigation results:
CXR – normal
HIV ELISA positive – still good CD4-count (>25%)
LP – CSF: 2 polymorphs, 46 lymphocytes, protein >2 g/L and glucose 2.1 mmol/L
CT-scan: Basal enhancement, hydrocephalus and periventricular oedema
- TB Meningitis Stage 2B



Lessons case 2

- Importance of taking a proper (detailed) history!
 - Mother HIV-infected, child tested?
 - Mother TB – no IPT – missed opportunity!
 - Often 3-4 visits to health institutions BEFORE diagnosis of TBM is made, as non-specific complaints (headache, low-grade fever, apathy/lethargy, vomiting, TB source case, FTT/LOW) and children not clinically examined (weight gain, neck stiffness)



- Need high index of suspicion, good clinical history and ask about known source case with TB

Diagnosis of TB in children: Conventional approach

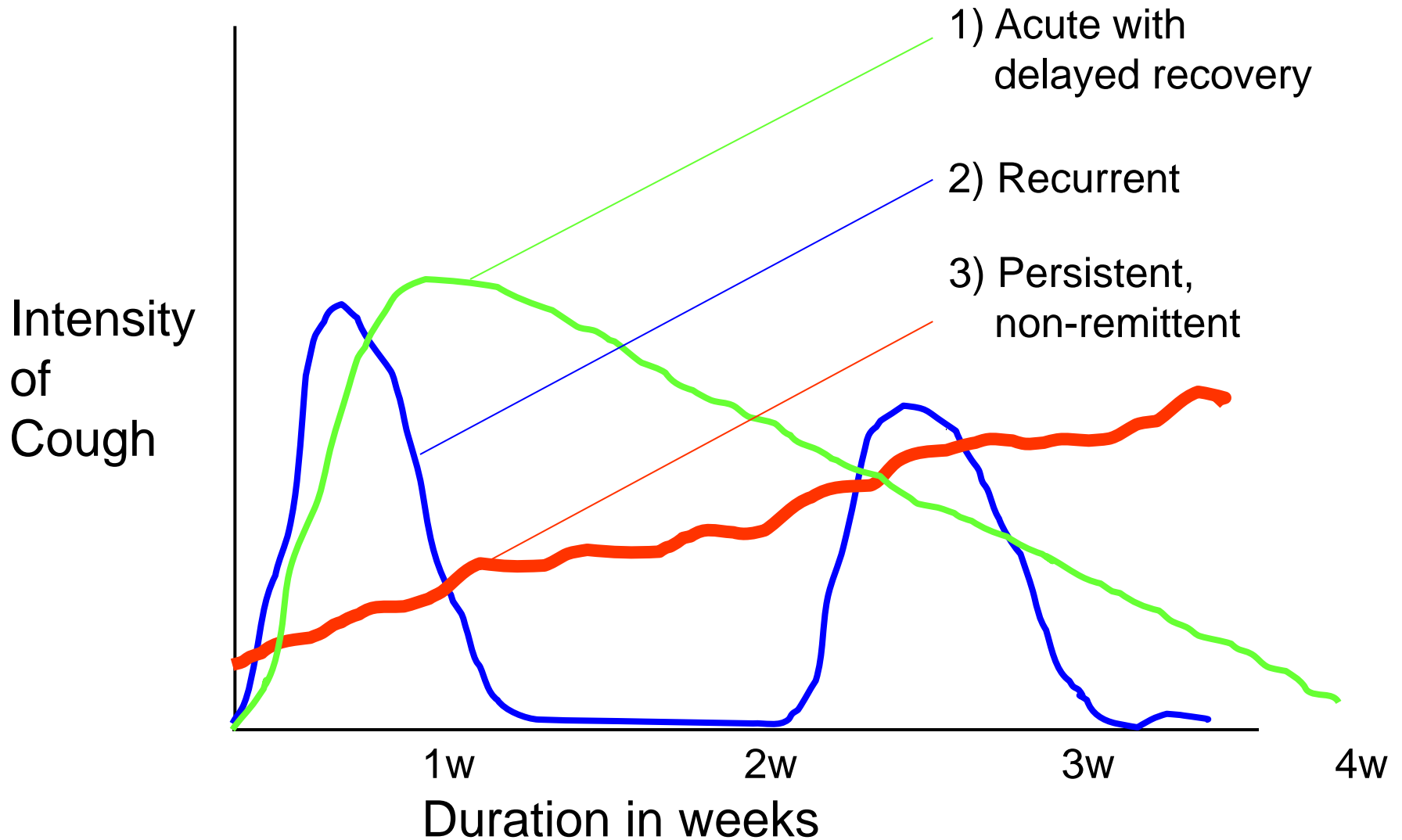
A constellation of the following:

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

History of symptoms / TB contact

- Symptoms:
 - Well-defined symptoms give improved yield
 - Chronic cough = unremitting cough >2-3 weeks
 - Fever = >7-14 days not responding to AB
 - Weight loss or FTT = documented (RTHC)
 - Fatigue (tiredness) – not keeping up with others
- In some children TB presents as an acute pneumonia; both in HIV-infected and –uninfected
- History of TB contact: Any close contact with an infectious TB case in the last year. Drug-resistant?

Symptom characteristics



Courtesy Ben Marais

Bacteriological confirmation

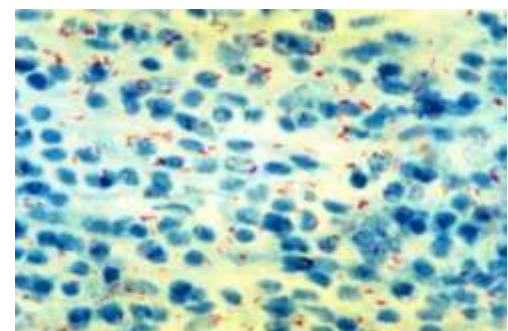
- The majority of child TB cases are diagnosed without bacteriological confirmation
- **If DST of adult source case is known, treat child contact according to adult source case isolate's DST result, as concordance between source and child's isolates is 78-90%**

Why do we need bacteriological confirmation?

- **To confirm TB in difficult cases**, e.g. uncertain lung pathology, HIV-infected children, extrapulmonary TB
- **To confirm drug resistance if a source case has DR-TB**
- **To determine DST in children with unknown source cases, or if source cases have poor response to first-line treatment with unknown DST**
- **If child responds poorly to adherent TB treatment**

Which specimens in children?

- **The more specimens and the better the quality, the higher the yield (preferably before starting treatment unless TBM)**
- Respiratory samples in children:
 - Induced sputum ~ gastric aspirate
 - Expecterated sputum in older children
 - NPA, tracheal aspirates or BAL
- FNA biopsies are very useful for diagnosis of EPTB
- CSF, pleural/pericardial/ascitic fluid, surgical biopsy specimens, ear swabs, stool / urine – Xpert and culture (M.tb)



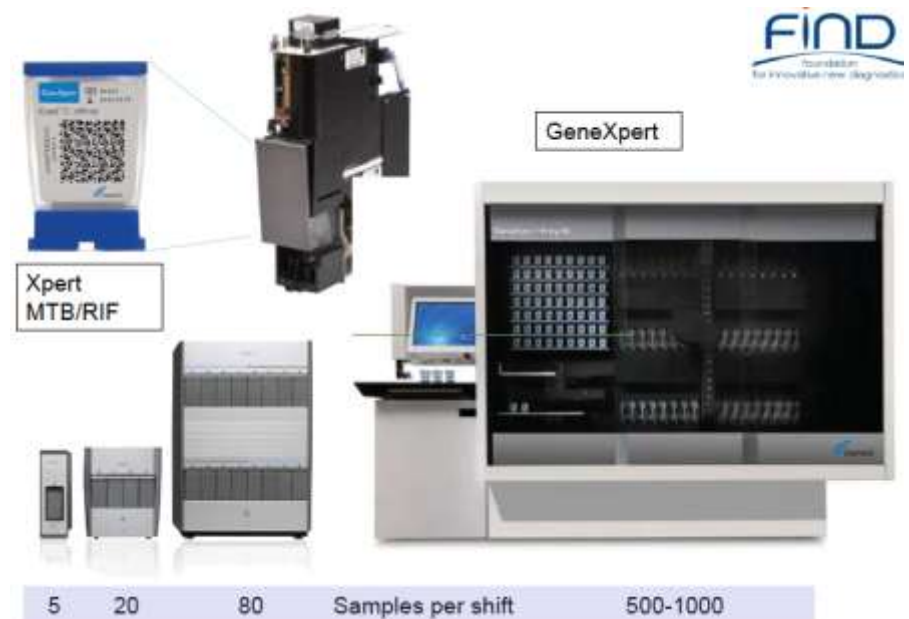
Incremental yield of multiple tests: CSF in TB meningitis as example

	TBM (n)	Non-TBM (n)	Sensitivity	Specificity
Total no of subjects	56	45		
Fluorescence microscopy	2	0	0.04	1.00
MGIT	12	0	0.21	1.00
Fluorescence microscopy/MGIT	12	0	0.21	1.00
MTBDR <i>plus</i>	18	1	0.32	0.98
Xpert	14	0	0.25	1.00
MGIT/ MTBDR <i>plus</i>	25	1	0.45	0.98
MGIT/Xpert	21	0	0.38	1.00
MTBDR <i>plus</i> /Xpert combined	27	1	0.48	0.98
MTBDR <i>plus</i> /Xpert/MGIT combined	31	1	0.55	0.98

Courtesy, Regan Solomons, Cape Town

Xpert MTB/RIF (GeneXpert)

- Xpert MTB/RIF replaces smear microscopy, not culture!
- Detection threshold 130-150 CFU/ml
- Xpert MTB/RIF provides only DST for RIF
- With increasing numbers of RIF-monoresistant TB cases in adults and Xpert MTB/RIF results only, managing child contacts is a problem
- Xpert can be done on sputum, GAs, FNA of LN, CSF and other!



2013 WHO Policy Update: Xpert MTB/RIF for children


- 13 paediatric studies, 2603 children:
- Sensitivity of Xpert vs. culture for *M. tuberculosis* detection from respiratory samples: 66% (Specificity 98%)
- Sensitivity of Xpert vs. culture for detection of rifampicin resistance: 86% (Specificity: 98%)
- For pulmonary TB in children:
- “Xpert MTB/RIF **should** be used ... as the initial diagnostic test in children suspected of having **MDR-TB or HIV-associated TB** (*strong recommendation, very low quality evidence*)”

EPTB in children: Xpert vs. culture

Specimen	Sensitivity	Specificity
CSF	80	99
Pleural fluid	44	98
Gastric fluid	84	98

- Xpert **should** be used ... as the initial diagnostic test for **CSF** specimens (strong recommendation, very low quality of evidence)
- Xpert **may be used** as a replacement test for specific **non-respiratory specimens** [for] extrapulmonary TB (conditional recommendation, very low quality of evidence)

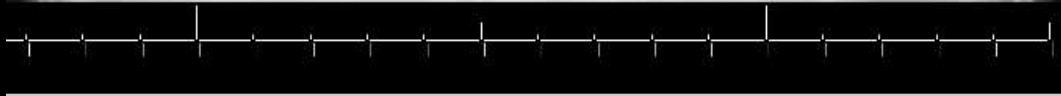
Role of Xpert MTB/RIF in diagnosing child-TB

- Children mainly smear-negative TB, and Xpert only positive in 60-70% of sm-/cult+ PTB cases
- Where labs work well and specimen quality is good, culture yield in child TB cases = 30-40%, whereas Xpert yield will be 20-27%
- Therefore: 
 - Culture yield better than Xpert yield and provides more DST results with well-functioning labs
 - Negative Xpert or culture does not exclude TB in children

Case 3

- At 18 months of age boy had smear-positive, cavitory TB LUL. No culture or DST done. Weight 7.9 kg
- Started on 1 tab Rimcure (30/60/150 – H/R/Z)
- Despite DOT deteriorated clinically – at 2 months on treatment lost weight, still cavities LUL. Culture and DST done, but no follow-up of culture (which was INH-resistant)
- 5 months on treatment – presented with further LOW and convulsions and stage 3 TBM diagnosed, now MDR-TBM!
- Only known source case uncle with DS-TB

Case 3

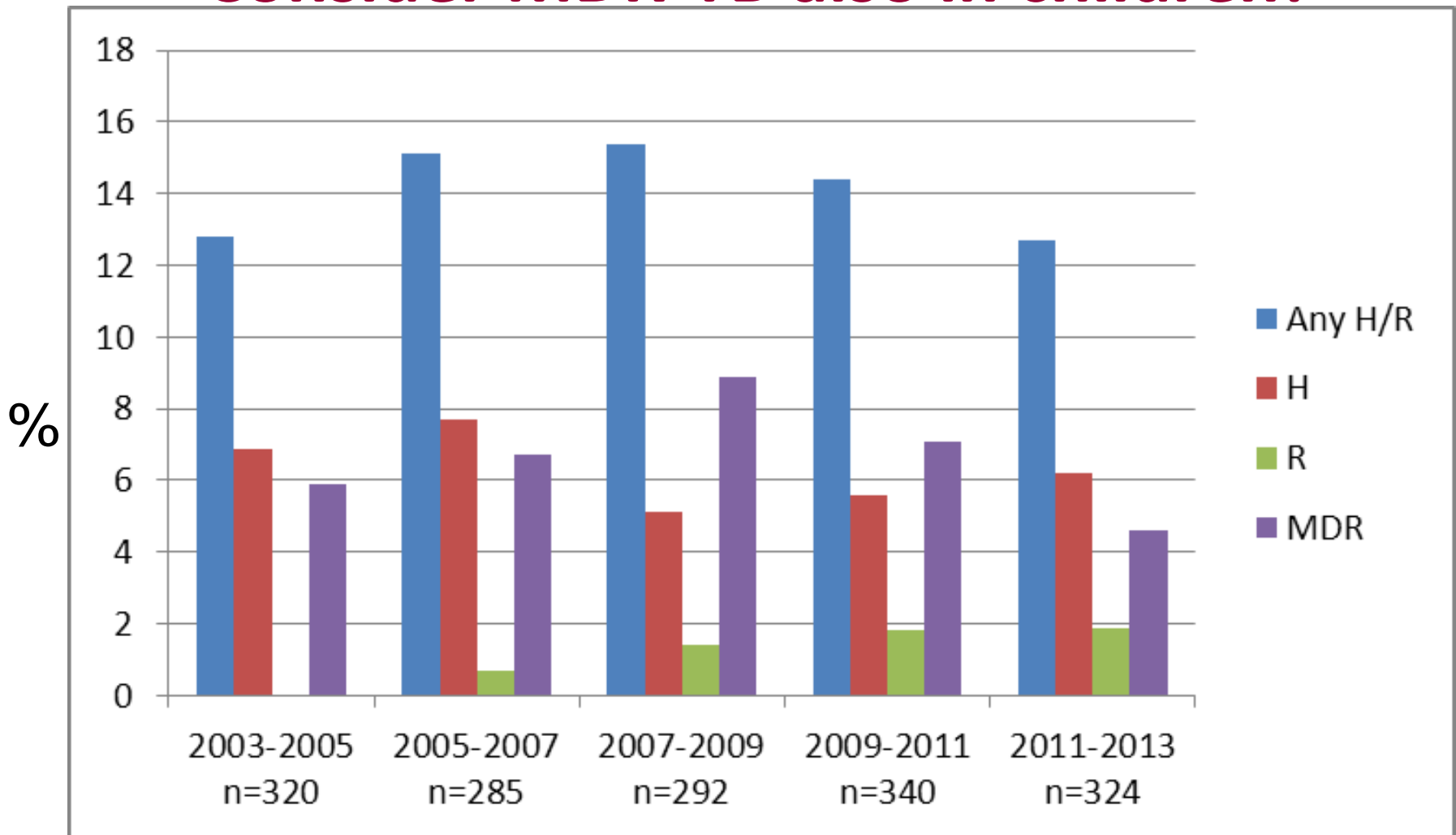




Lessons learned case 3

- Treat TB with **APPROPRIATE regimens** and **APPROPRIATE dosages** of anti-TB drugs, otherwise poor response to treatment with further extension of TB (e.g. TBM) and, although this is an exceptional case in a young child, development of drug-resistant TB
- Smear-positive / extensive pulmonary TB / severe forms of extrapulmonary TB / HIV-TB – treat with 2HRZE/4-7HR - dosages 10/15/35/20mg/kg
- TBM treatment new SA guidelines:
HRZEth at 20/20/40/20mg/kg for 6-9 months

Consider MDR-TB also in children!



Trends of drug resistance in childhood TB at Tygerberg Hospital, Western Cape, 2003 - 2013

Case 4

- 5-year-old boy referred on 1/2/08 with a spinal deformity (gibbus)
- No TB contact history and negative Mantoux
- MRI – cold abscess and spinal TB at T8/T9
- Started 2RHZE; treated as inpatient for 2 months and then converted to continuation phase RH - Sent home to continue treatment
- Follow up very intermittent, but adherent treatment
- Minimal improvement – worsening kyphosis noted
- Second MRI 20/3/09 (13 months later)
- Regimen 2 started – no improvement



Case 4

- Surgery 30/4/09: Specimens from bone and pus AFB positive, but culture negative
- 1/5/09 due to deterioration on regimen 2 started on MDR regimen
- In June 09 on re-taking history – caregiver (aunt) MDR-TB in 2008!



- **MDR-TB diagnosis in children:**
 - Culture and DST (genotypic or phenotypic) DR-TB
 - Source case has DR-TB (also MDR/XDR-TB)
 - Not responding to adherent first-line therapy

Communication Hospital/Clinic/Health Dept

- Transfer from hospital to clinic – many patients lost
- Recording/reporting in electronic register of culture-confirmed cases in Cape Town: only 60% captured – missing serious cases (TBM cases and deaths)!
- With active intervention – identifying children with TB, giving letters and contacting clinics improved recording and reporting as well as treatment continuation



- Morbidity and mortality increase due to poor communication between institutions
- No stats – no resources!!!



Conclusions

- TB is common – ALWAYS have a HIGH INDEX OF SUSPICION, even in very young infants
- Take a proper HISTORY – it is 70% of diagnosis!
- Beware of the CAREGIVERS accompanying children – they may have undiagnosed TB (infection risk)
- TBM – initial presentation non-specific, but high morbidity/mortality if missed –
History/Examination!



Conclusions (2)

- Xpert MTB/RIF is wonderful – but be aware of serious limitations. Replaces smear-microscopy, not culture
- Treatment – use correct dosages and regimens
- DR-TB in children: Know when to suspect and TREAT!
- Communication essential for treatment completion and recording and reporting for resources!

Thank you

