Screening, Diagnosis and Management of MDR-TB in Children

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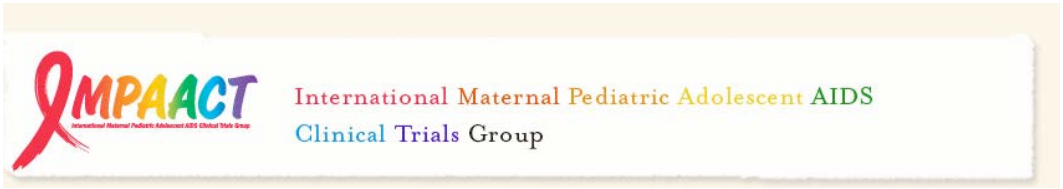


Definitions in DR-TB

- Mono-drug resistance: Resistance to single drug
- (RIF-mono-resistant TB – RIF-R/INH-S
- Poly-drug resistance: Resistance to 2 or more drugs, but not to both INH and RIF
- MDR TB: Resistance to INH & RIF (+/- other drugs)
- Pre-XDR TB: MDR plus FQN or SLID resistance
- XDR TB: MDR & resistance to a 2nd-line injectable drug & a fluoroquinolone

Rationale for preventive treatment

- Prophylactic treatment is given after exposure to prevent TB infection, and treatment given after TB infection is intended to prevent progression to TB disease.
- Preventive treatment includes both these situations
- **To provide preventive treatment**
  - contact with a source case and risk of infection needs to be established and
  - TB disease should have been excluded

History of contact

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

The individual risk assessment should take into consideration the following:

- TB contact's risk for progression to TB disease (e.g. age, immune status, immunosuppressive Rx)
- Infectiousness of the source case (Pulmonary vs Extrapulmonary TB; Smear and/or culture-positive)
- Closeness and duration of contact with the source case (same house/bedroom; same yard; visits only?)
- Whether there is one or more source cases (could have different DSTs)
- The DST pattern(s) of the source case(s)
- The risk for adverse events upon initiating preventive therapy

There is no gold standard to detect *M. tuberculosis* infection

- **A household contact score was developed – based on 10 questions in 4 groups:**

  Proximity, Duration, Intensity of M.tuberculosis exposure and number of source cases

  This *correctly* predicted 70% of TST and IGRA-positive children 0-5 years of age with household TB exposure

Mandalakas et al. IJTLD August 2012

How to investigate contacts

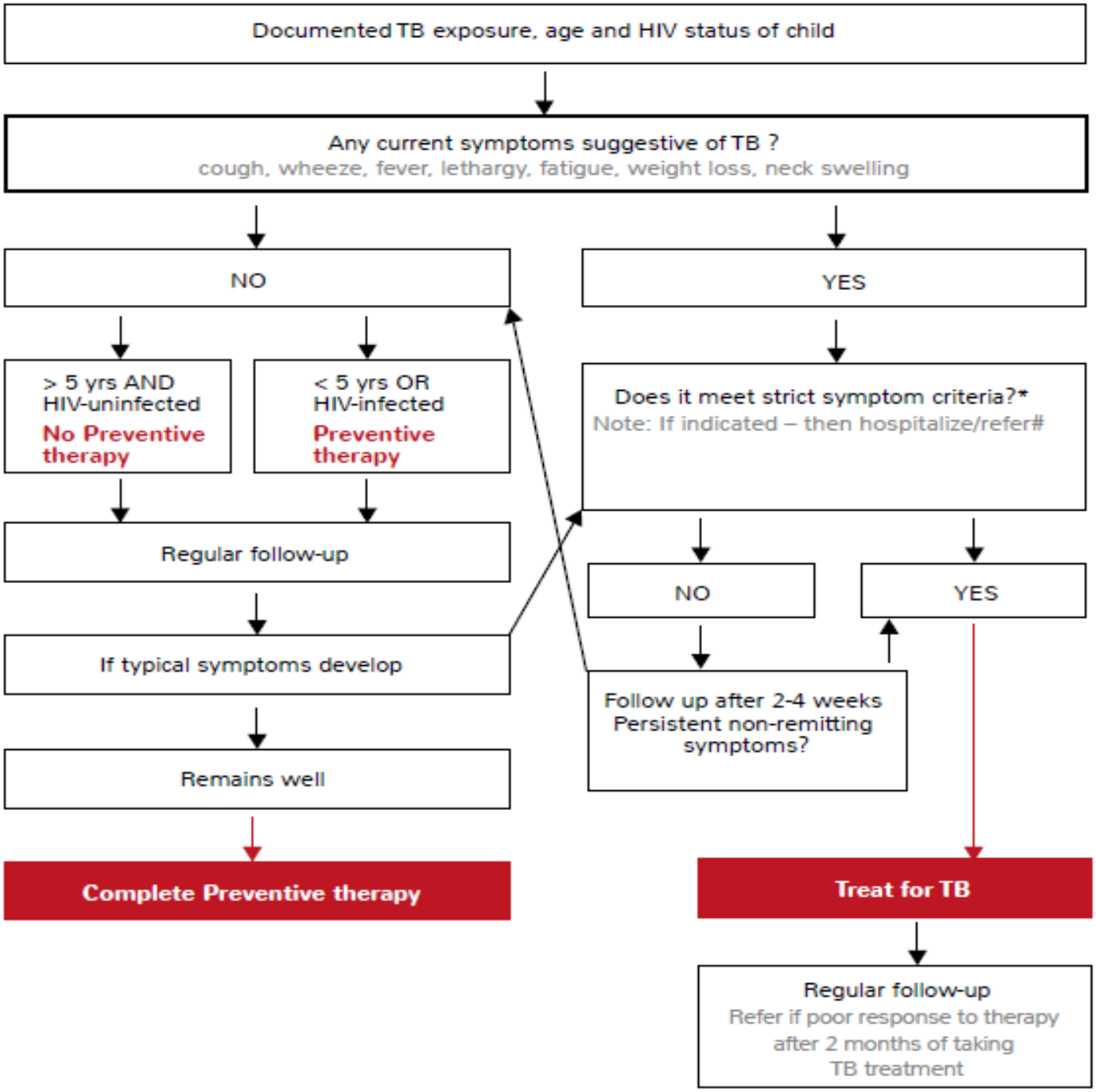
Clinical assessment:

- History (**Symptoms – not only chronic symptoms**; closeness and duration of contact; **DST** of source case's isolate)
- Clinical examination (PTB/EPTB): Clinical assessment alone is sufficient to decide whether contact is well or symptomatic (low resource settings)

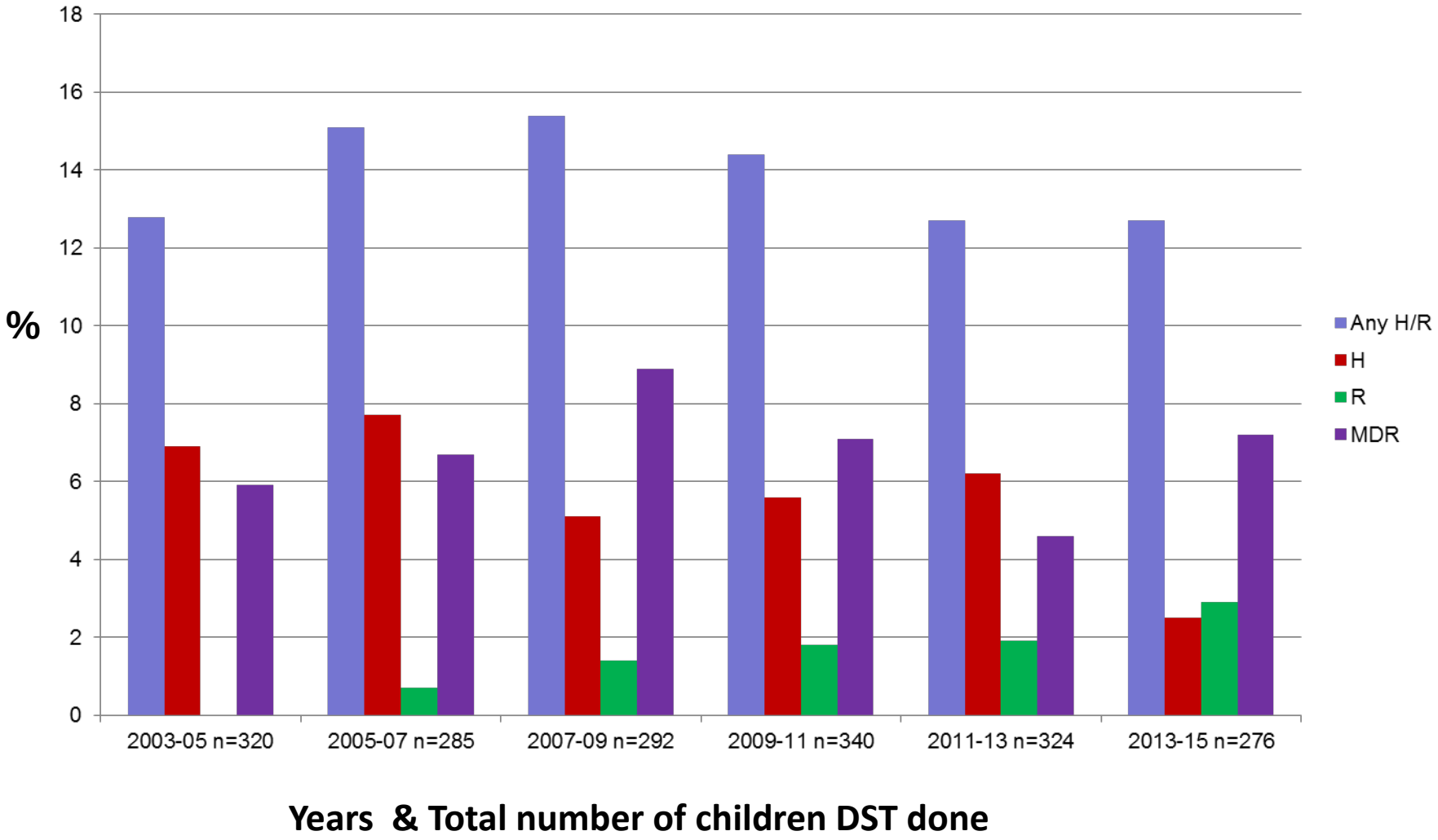
THE UNION'S DESK GUIDE FOR DIAGNOSIS AND MANAGEMENT OF TB IN CHILDREN 2016

However for research need more:

- TST (IGRA) – **even if TST/IGRA is negative and exposure has been confirmed**, **preventive Rx is indicated (if no TB disease)**
- CXR (for diagnosis of disease) – or other imaging/tests
- If TB disease suspected (contact symptomatic or has abnormal CXR) – **specimens for culture/DST before Rx**


Documented TB exposure, age and HIV status of child
Any current symptoms suggestive of TB ?
cough, wheeze, fever, lethargy, fatigue, weight loss, neck swelling
NO
YES
> 5 yrs AND HIV-uninfected
No Preventive therapy
< 5 yrs OR HIV-infected
Preventive therapy
Does it meet strict symptom criteria?*
Note: If indicated – then hospitalize/refer#
Regular follow-up
NO
YES
If typical symptoms develop
Follow up after 2-4 weeks
Persistent non-remitting symptoms?
Remains well
Complete Preventive therapy
Treat for TB
Regular follow-up
Refer if poor response to therapy after 2 months of taking TB treatment

Trends of DR in childhood TB: WC



MDR/XDR-TB in children

- Is mainly new (transmitted) drug resistance from infectious source cases with MDR/XDR-TB (even if treated before – more likely transmitted))
- Is more difficult to acquire because of the paucibacillary nature of primary disease, but it is possible with cavitary pulmonary disease in mainly older children/adolescents
- In our experience DR-TB is not less infectious and may cause almost as much disease than DS-TB
- Disease (>90%) in children usually develops within 12 months after infection

Diagnosis : M/XDR-TB in children

- DR TB is a **microbiological diagnosis**
- In children often difficult (paucibacillary TB):
  - **Confirmed** if DR *M. tuberculosis* strain is isolated from a child (and has TB disease)
  - **Probable** DR-TB if known contact with an adult DR PTB case (>78-90% concordance in several studies)
  - Possible DR-TB if: (excluded from study)
    - a child gets worse on Rx, failing adherent Rx
    - an adult source case with unknown DST result is a treatment failure, a retreatment case or died of TB during adherent Rx

Bacteriological confirmation

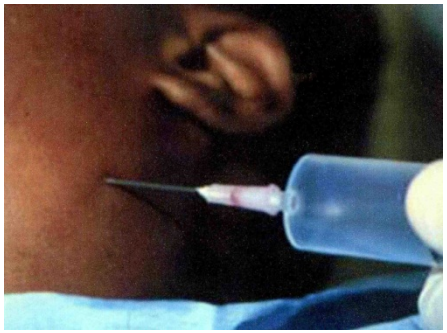
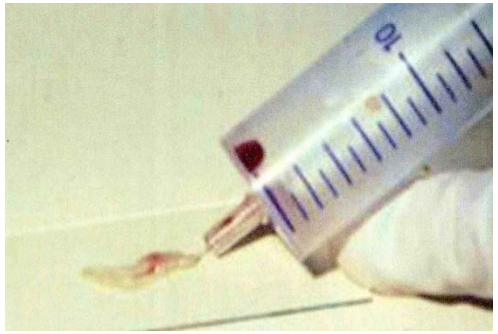
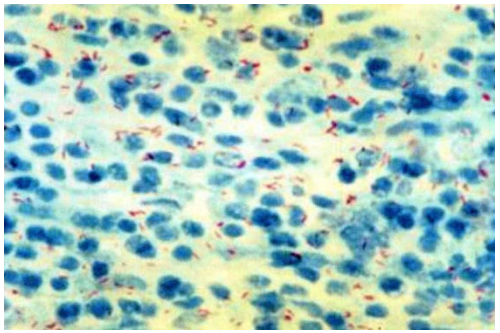
- The majority of child TB cases are diagnosed without bacteriological confirmation
- **If DST of adult source case is known, treat child contact according to adult source case isolate's DST result, as concordance between source and child's isolates is high**

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 with DR-TB is identified**
- **To determine DST in children with unknown source cases**, especially if they have poor response to first-line treatment

Culture for *M. tuberculosis*

- Obtain specimens for culture/DST BEFORE starting ANY treatment (only in TBM or miliary TB it is essential to start treatment urgently)
- Respiratory samples in children:
  - Induced sputum ~ gastric aspirate (similar yield)
  - 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)

Principles of childhood MDR-TB Rx

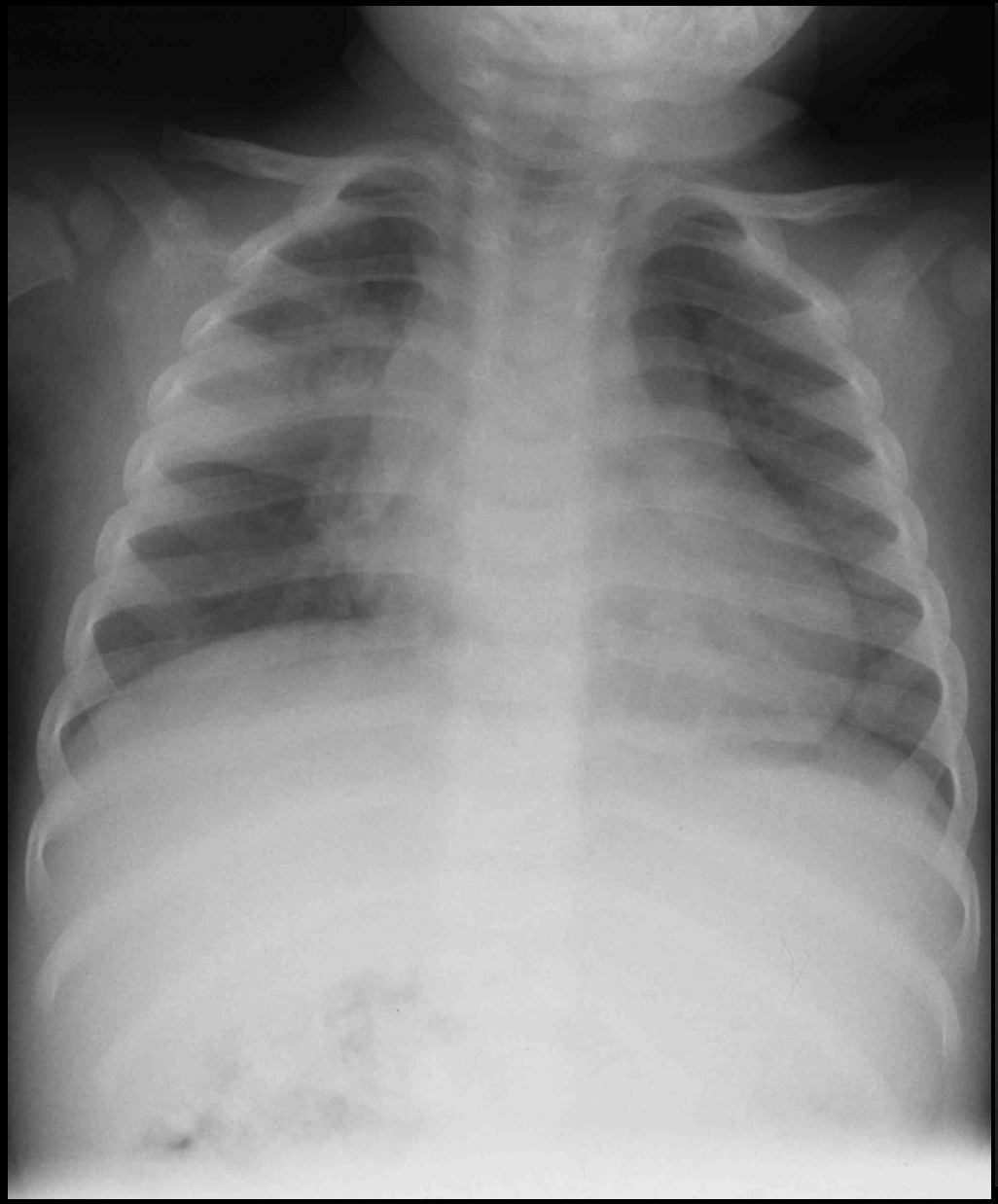
- Confirm the MDR-TB in the child if at all possible
- If MDR-TB is confirmed, also do DST for 2nd-line drugs
- Management – at a specialized MDR-TB clinic
- Use the adult index case's isolate DST pattern if no isolate from child is available. (Standardised MDR-TB treatment if empirical treatment for treatment failure)
- Give directly observed therapy (DOT) with daily treatment in DR-TB
- Counsel patients/parents at every visit for support, about adverse events, and importance of adherence
- Follow-up is essential; clinical, radiological and cultures

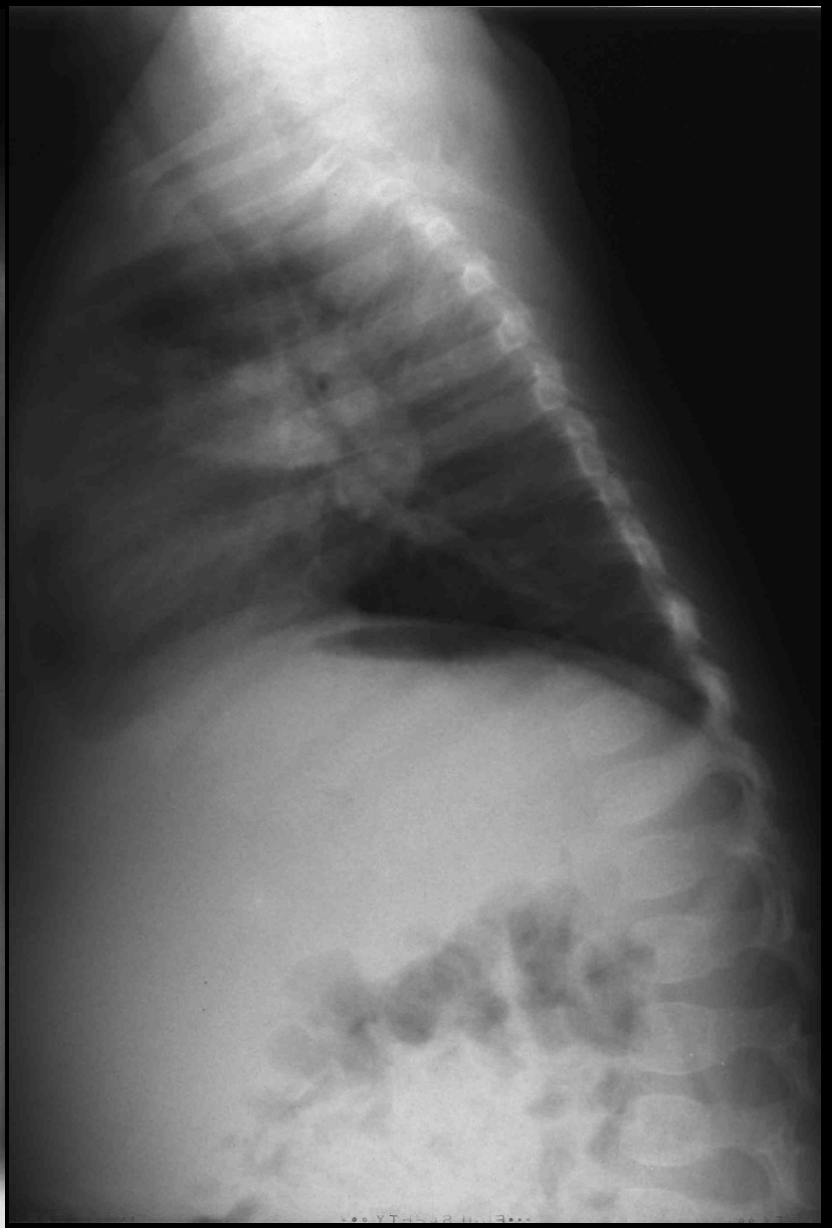
Principles of childhood MDR-TB Rx

- Give 4 or more drugs to which the patient's isolate is susceptible and/or naïve. Number of effective drugs depends on extent of disease and availability of drugs
- Drugs in previously failed regimen likely not effective
- Be aware of the different drug groups and cross-resistance (and co-resistance) amongst these drugs
- 2nd-line drugs are generally more toxic than 1st-line drugs
- Adverse effects more difficult to assess in children, but screen regularly
- Not complete if I don't add: NEVER add one drug to a failing regimen

Case 1

- A 14-month-old boy presents as contact of grandmother (HHC/caregiver) who has 3rd episode of TB, now confirmed GXP-pos RIF-R
- Gaining weight >50th centile / >0 Z-score WfA
- Coughing only for one week
- Has been getting INH since grandmother was first diagnosed a month ago but then only smear-pos (no DST yet)
- Mantoux 20mm
- BCG scar positive
- What next?

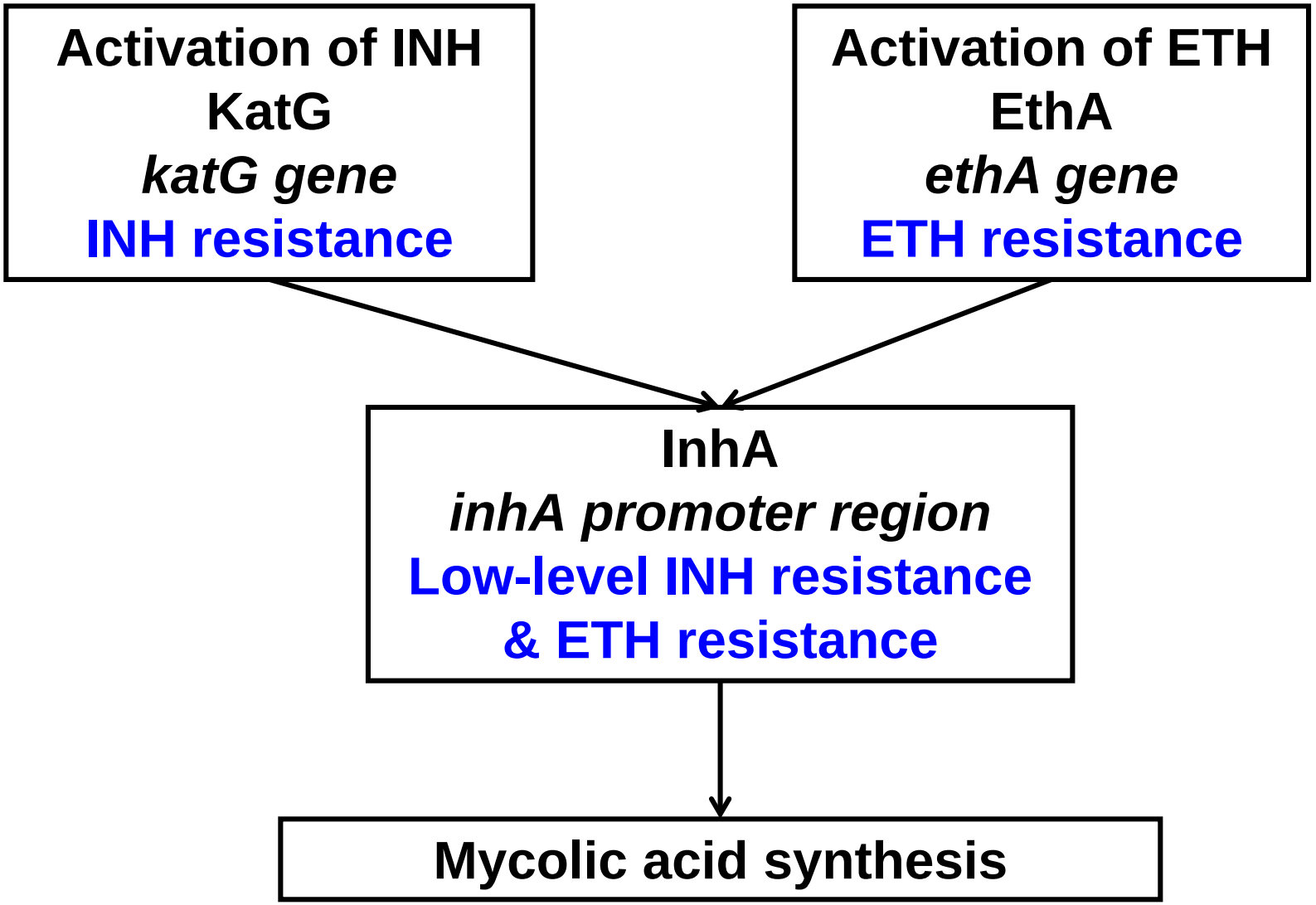




Case 1

- CXR: RUL opacification plus hilar nodes R
- **BEFORE treatment** obtain specimens for culture/DST (uncle in house had DS-TB a year ago!)
- Be sure to follow up on grandmother's culture and DST!
- What treatment would you start the child on?
  - which drug regimen?
  - what duration of intensive/continuation phase Rx?

INH and Ethionamide co- and cross resistance



Building a regimen for MDR/XDR-TB

- Group A: A Fluoroquinolone – levofloxacin or moxifloxacin
- Group B: A 2nd-line injectable drug – kanamycin, amikacin or capreomycin (high rates of cross-resistance)
- Group C: Other core drugs in combination:
  - Ethionamide/Prothionamide (*inhA* mutation?)
  - Cycloserine/Terizidone
  - Clofazimine
  - Linezolid
- Group D1: Add-on drugs (not counted as effective drugs?)
  - high-dose INH (low-level INH resistance / *inhA* mutation)
  - pyrazinamide; ethambutol
- Group D2: New drugs: Delamanid; Bedaquiline
- Group D3: PAS; Amoxiclav plus Carbapenem

Case 1

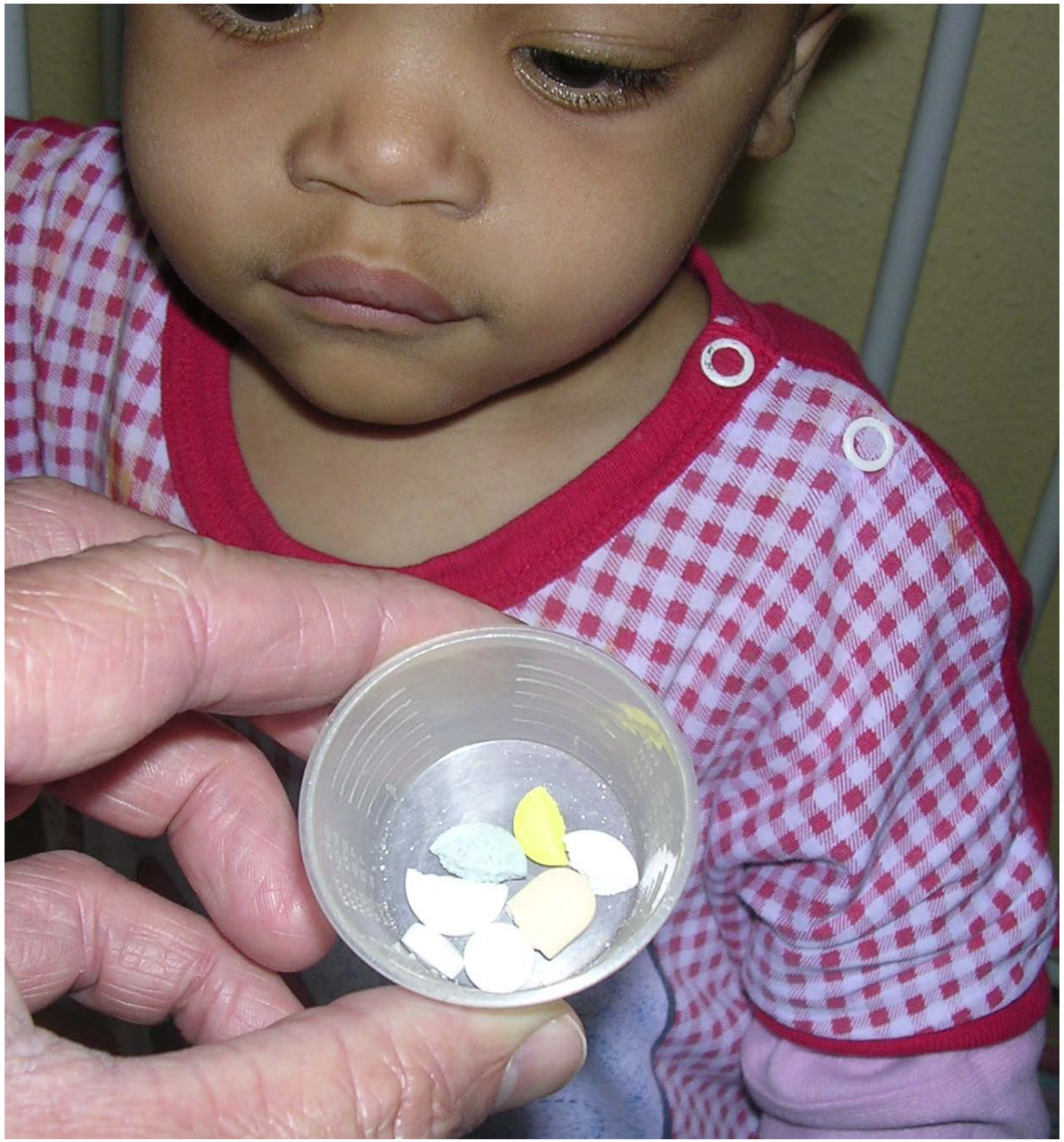
Treatment options (grandmother likely source case):

- 4-6Lfx/Am/Z/E?/Cs-Trd/hdH/Eto – 8-12Lfx/Z/E/Cs-Trd/hdH/Eto (Standard Rx – duration decided by response to treatment/extent of disease)
- Because at this point no DST for H or second-line drugs, difficult to use new shorter regimen; however, could drop Cs-Trd and replace with Cfz initially and decide once other DST results known

- Child's initial culture result: LPA – INH and RIF resistant (*katG* mutation)
- Grandmother: INH/RIF/Am resistant – FQN suscept
- Change Rx? How many active drugs in current regimen?

Case 1

- If we change treatment, consider the following:
  - How long has the child been on the current regimen?
  - Is the child doing well clinically or is he failing therapy?
  - Compare the DSTs of source case and child's isolates – same INH conferring mutation/second-line DST (if available)?
  - Is three effective drugs sufficient for this child BUT also consider bactericidal/bacteriostatic drugs (how effective are the drugs?)
  - Which drugs should we STOP because they don't add value and may cause harm
  - Which drugs do we have available to add – preferrably not adding a single drug, although possible if NOT a failing regimen/Rx <1 month



Absence of child-friendly drugs and dosages

11-month-old with morning tablets MDR-TB Rx

Difficult to accurately break tablets to correct dosage.

Also receives an injectable

WHO MDR-TB drug grs	Recommended doses	CSF penetration
Gr. A Fluoroquinolones		
Levofloxacin	15-20 mg/kg (higher?)	Moderate to good (60-80%)
Moxifloxacin	10 mg/kg (PK studies?)	
Gr. B 2nd-line Inject Km/Am/Cm	18-20 mg/kg	Poor (<20%)
Gr. C: Other core 2nd-line drugs		
Ethionamide /Pto	15-20 mg/kg	Good
Cycloserine / Tzd	15-20 mg/kg	Good
Linezolid	<10 yrs: 10mg/kg bd >10 yrs: 300-600mg/day	Good
Clofazimine	2-5 mg/kg; max 100mg (alternate day dosing?)	Poor

WHO MDR-TB drug groups	Recommended dose	CSF penetration
Group D: Add-ons D1:		
Pyrazinamide	30-40 mg/kg	Good
Ethambutol	20-25 mg/kg	Poor (<20%)
High-dose INH	15-20 mg/kg (400mg)	Good
D2: Bedaquiline	**>12 yrs >33kg as in adults 400mg/dx2w-200 3x/w**	Likely Poor
Delamanid	**>6yrs/>20kg - 50mg bd >12yrs/>35kg - 100mg bd**	Likely Poor
D3: PAS	150-200 mg/kg/day	Poor – single dose for C_{max}
Amox/Clav with imipenem/meropenem	25-30mg/kg tds IV as per bacterial infection	Poor

WHO new shorter regimen for RMR/MDR-TB

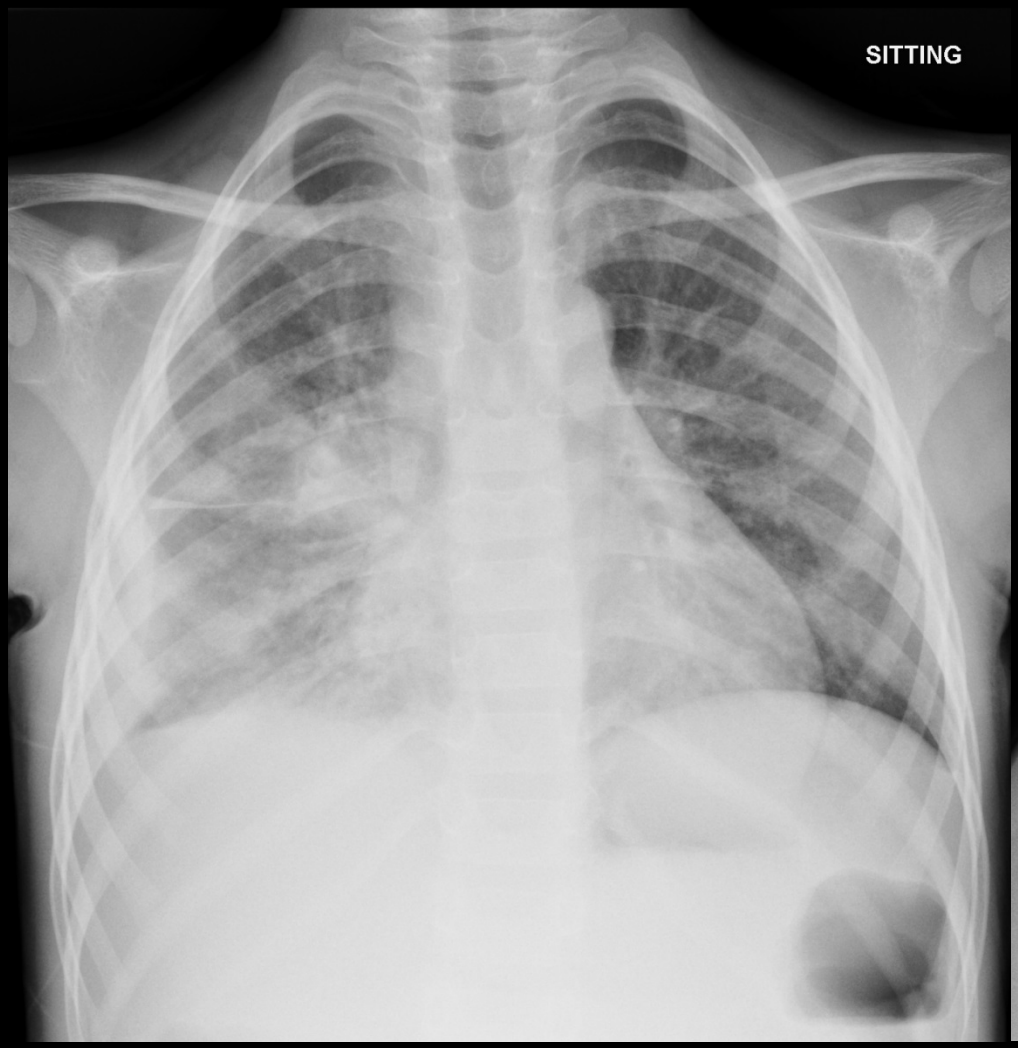
- ONLY for RMR-TB or strictly MDR-TB (INH+RIF resistance, no fluoroquinolone or second-line injectable drug resistance). Only PTB and should not have been treated for MDR-TB before
- 9-12 month regimen (depending on response to treatment)
- 4-6 Km Mfx Cfz H-hd E Pto Z / 5-6 Mfx Cfz E Z
- Not yet accepted in South Africa (discussed) as high rates of ethambutol and pyrazinamide resistance in MDR-TB cases
- Reason to mention is that MDR-TB treatment scene is CHANGING!

Case 2

- 6 yr 5 month-old girl-child was evaluated by ENT for cochlear transplant because of severe hearing loss.
- Deafness due to previous septic meningitis
- Noticed that patient was coughing (>2 weeks) and on history was losing weight – confirmed in RTHB
- Had previous TB in 2011 – treated for 6/12 (completed)
- No known TB contact currently (2016)
- Received BCG at birth (RTHB)
- No history of exposure to HIV at birth
- Weight 16.2 kg (0/+1 z-score WfA); height on +2 z-score
- Generalised lymphadenopathy; hepar 2-3cm
- What are your thoughts/what tests would you do?

Case 2

- FBC: WCC 5.5, Hb 10.9g/dL, MCV 83.9, Pl 342
- HIV test: ELISA positive! (newly diagnosed)
- CD4=399 (16.8%); VL=14317 (log 4.16)
- CXR done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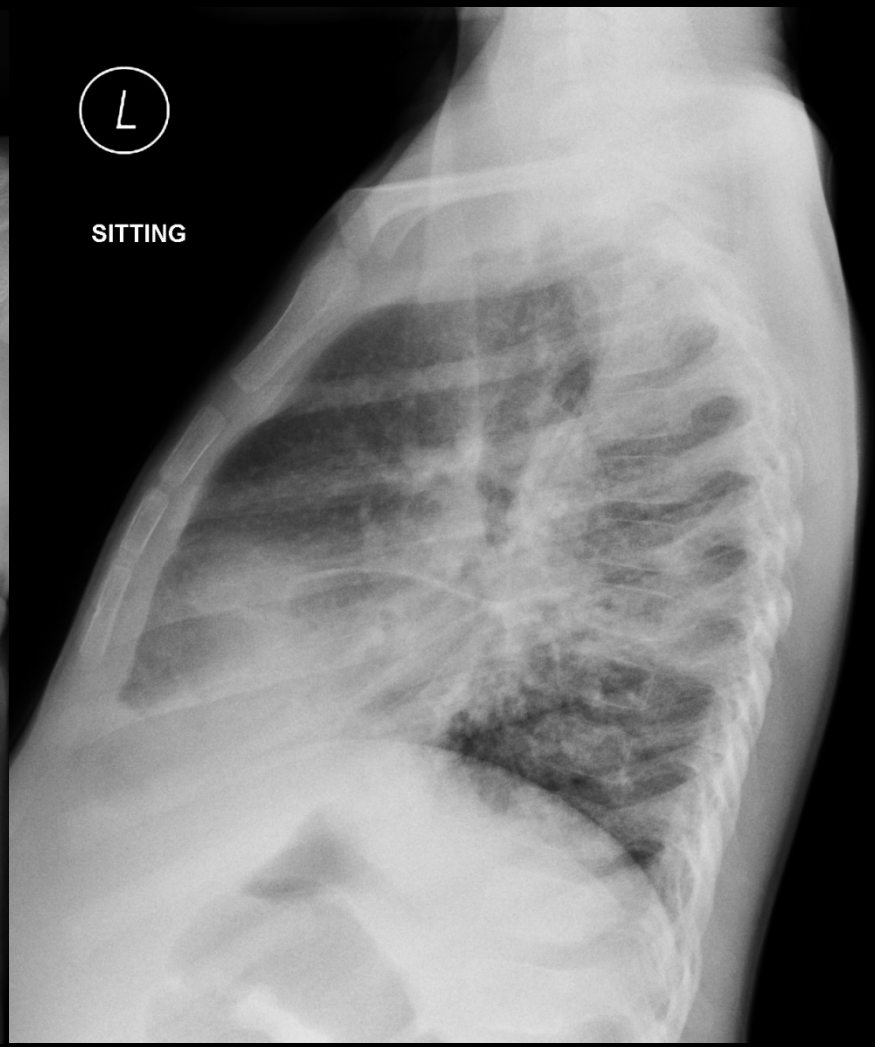
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Case 2

- Child's Gastric Aspirates were sent off BEFORE any treatment
- GXP-positive/RIF-resistant
- Mother also HIV-positive
- Mother's sputum: GXP-positive, RIF-resistant (diagnosed after child – reverse contact tracing)
- What should we consider and what treatment would you start in this child?

Case 2

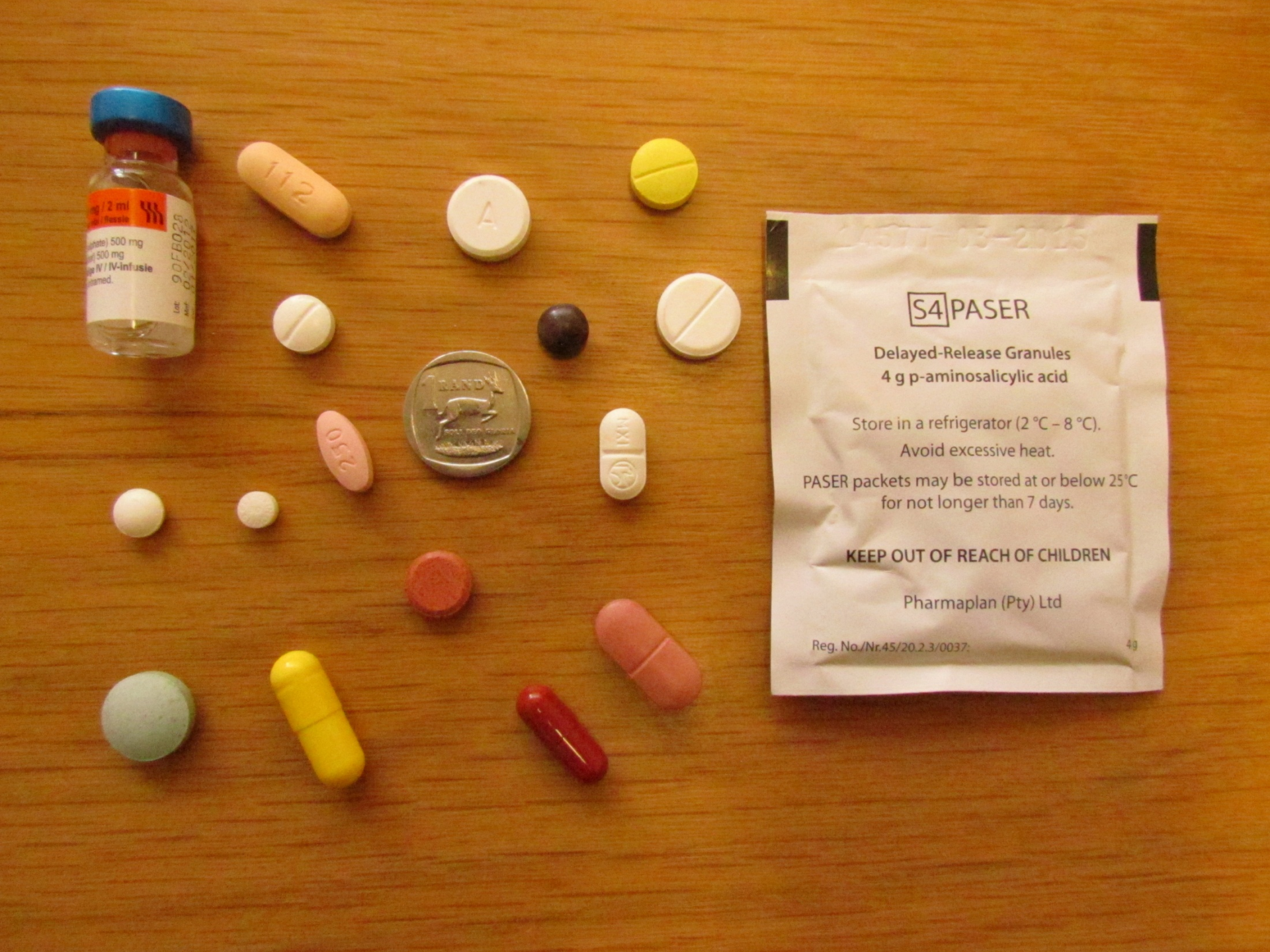
- Consider:
  - likely MDR-TB
  - child has profound hearing loss
  - HIV-infected
  - previous TB treatment although long ago!
- Started MDR-TB regimen:
  - hdINH/Eto/Z/E/Lfx/Tzd/Cfz/PAS – planning shorter regimen (no SLID)
  - ART 2 weeks later: 3TC/ABC/EFV
- Mother started on MDR-TB treatment (infectious risk)
- Later: Cult/DST: H+R+O-A- (inhA mut) – Child & Mother

Duration of treatment

- Optimal duration of treatment in children is not known – more paucibacillary disease, but also more often disseminated disease (consider penetration) than adults
- Cavitary or extensive pulmonary MDR-TB plus other resistance: as for adults 6 months intensive phase followed by 12-18 months continuation phase after first negative culture (depending on resistance e.g. XDR-TB current minimum 24 months)
- Primary, non-cavitary strictly MDR-TB - Often culture-negative (paucibacillary): Shorter regimen of 9-12 months treatment probably sufficient in children.
- Intensive phase including 2nd-line injectable drug, continuation phase mainly stop injectable drug – but WHO shortened regimen also drop other drugs (hdH/Eto)
- Aiming for a shorter/injectable-sparing regimens?

Adherence (and support)

- Treatment in hospital and in community needs to be observed – children are ingenious when it comes to making plans how NOT to take their treatment!
- Poor palatability of drugs may contribute to adherence problems
- Ask children/caregivers to identify the tablets/capsules and how many of each are taken – can check on dose as well (many mistakes made!)
- Communicate with HCWs who dispense the treatment – do they collect the drugs regularly or is there DOT?
- Pill counts and other methods may be useful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PASER packets may be stored at or below 25°C
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Adherence (and support)

- Most important: identify a reliable caregiver to provide the drugs and observe the child taking it
- Monitor adverse effects and address these, as could lead to non-adherence to treatment
- Teenagers – notoriously difficult group to adhere to treatment: Communication (clinic staff) and peer pressure (stigma/mocking) – both common problems
- Nutritional support and financial support often required by families – especially if caregivers or parents are also ill

Additional treatment

- Pyridoxine (Vit B6)
  Levels of B6 remain low in HIV-infected children despite multivitamin supplementation
  With terizidone and high-dose INH supplementation with pyridoxine recommended
  Cilliers K et al. Pyridoxal-5-phosphate plasma concentrations in children receiving tuberculosis chemotherapy including isoniazid. Acta Paediatr. 2010;99(5):705-710
- Cotrimoxazole
  Outcome of TB/HIV co-infected adults improved if given CTX preventive therapy. Role in TB treatment?
- Start ART within two weeks of starting MDR-TB treatment (watch out for IRIS especially TBM)
- Nutritional rehabilitation
- Corticosteroids (same indications as DS-TB

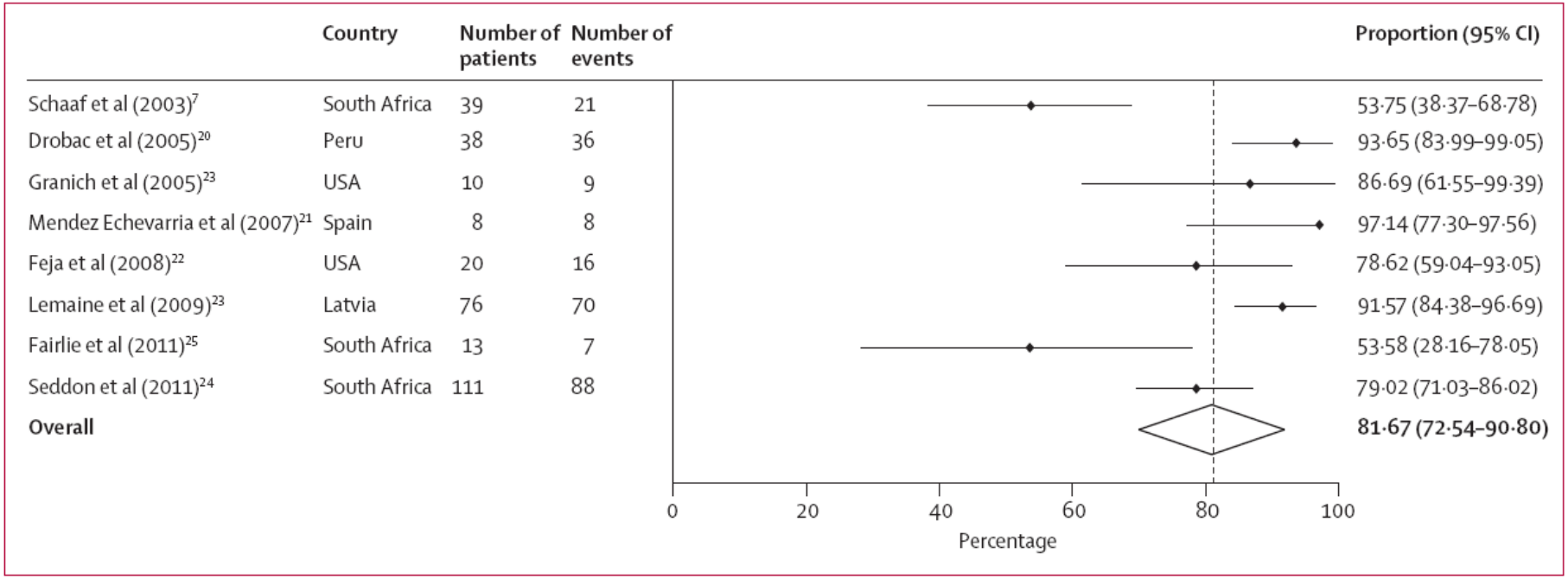
Drug-drug interactions

- Data on pharmacokinetic interactions between ART and the 2nd-line anti-TB drugs are incomplete, therefore unanticipated interactions may occur.
- The potential for clinically important changes in ART or anti-TB drug concentrations is less for 2nd-line anti-TB regimens compared to RIF-containing 1st-line regimens.
- ART and 2nd-line anti-TB drugs have many adverse effects in common.
- Risks attributable to the anti-TB/ART drug combinations vs. those due to potential confounding factors e.g. HIV infection itself, extent of immune suppression, co-morbidities (e.g. diabetes), concomitant medication and nutritional status, are uncertain.

Seddon et al. Tuberculosis 2012;92:7-12

Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis

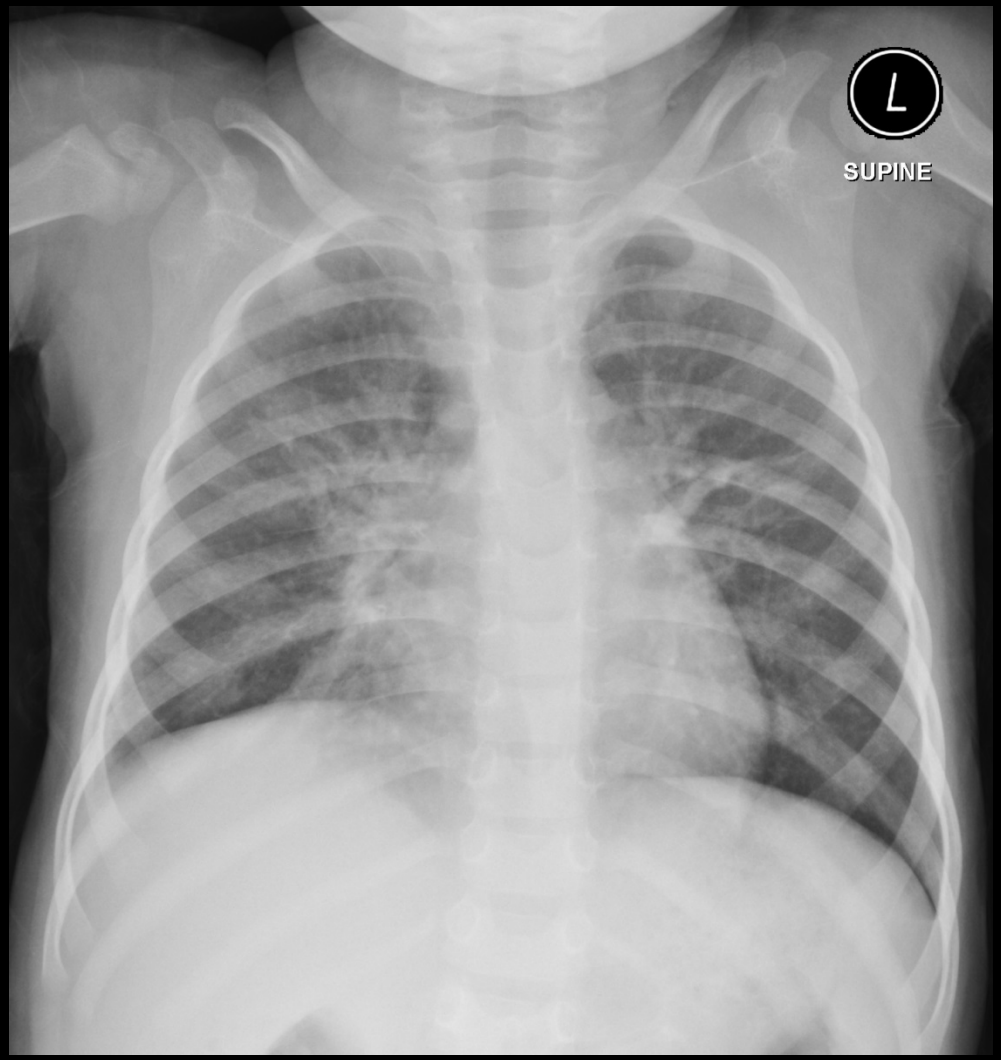
Dena Ettehad, H Simon Schaaf, James A Seddon, Graham S Cooke, Nathan Ford**



Lancet Infect Dis. 2012

Case 3

- 20-month-old girl: history of cough, fever, loss of weight (although weight >0 z-score WfA)
- No known source case according to mother
- Mantoux TST = 12mm
- HIV unexposed/HIV rapid negative
- CXR done
- Gastric aspirates sent for GXP/culture/DST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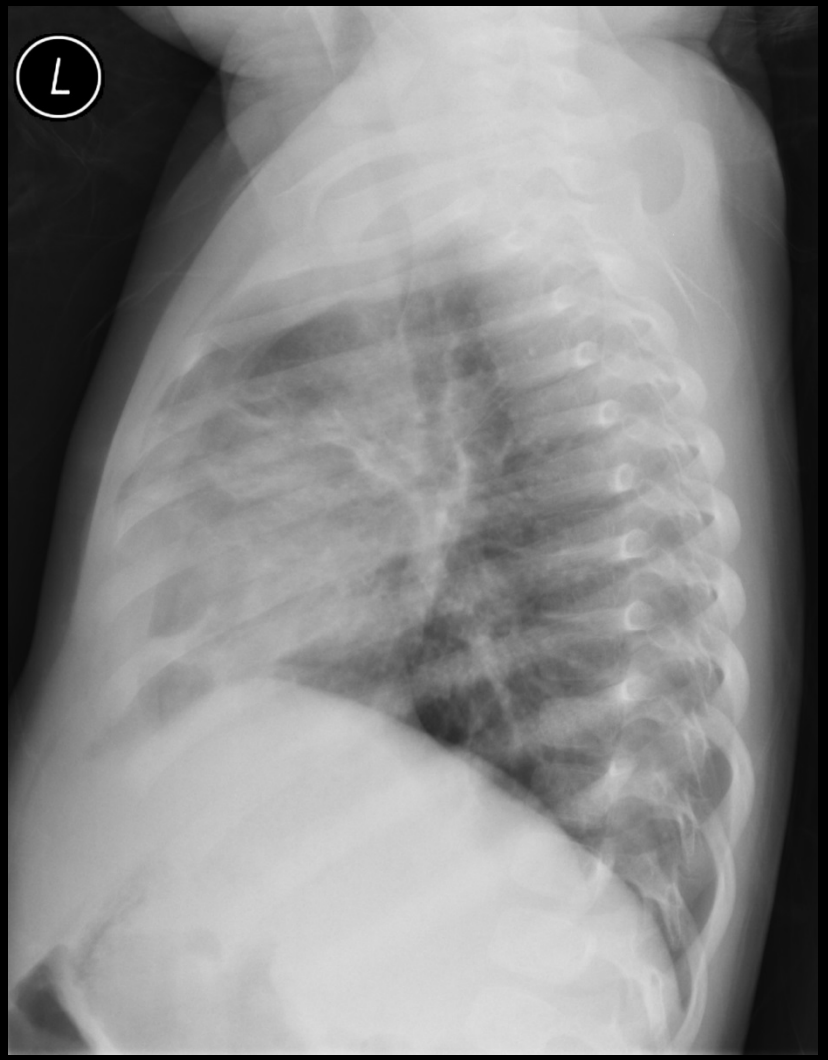
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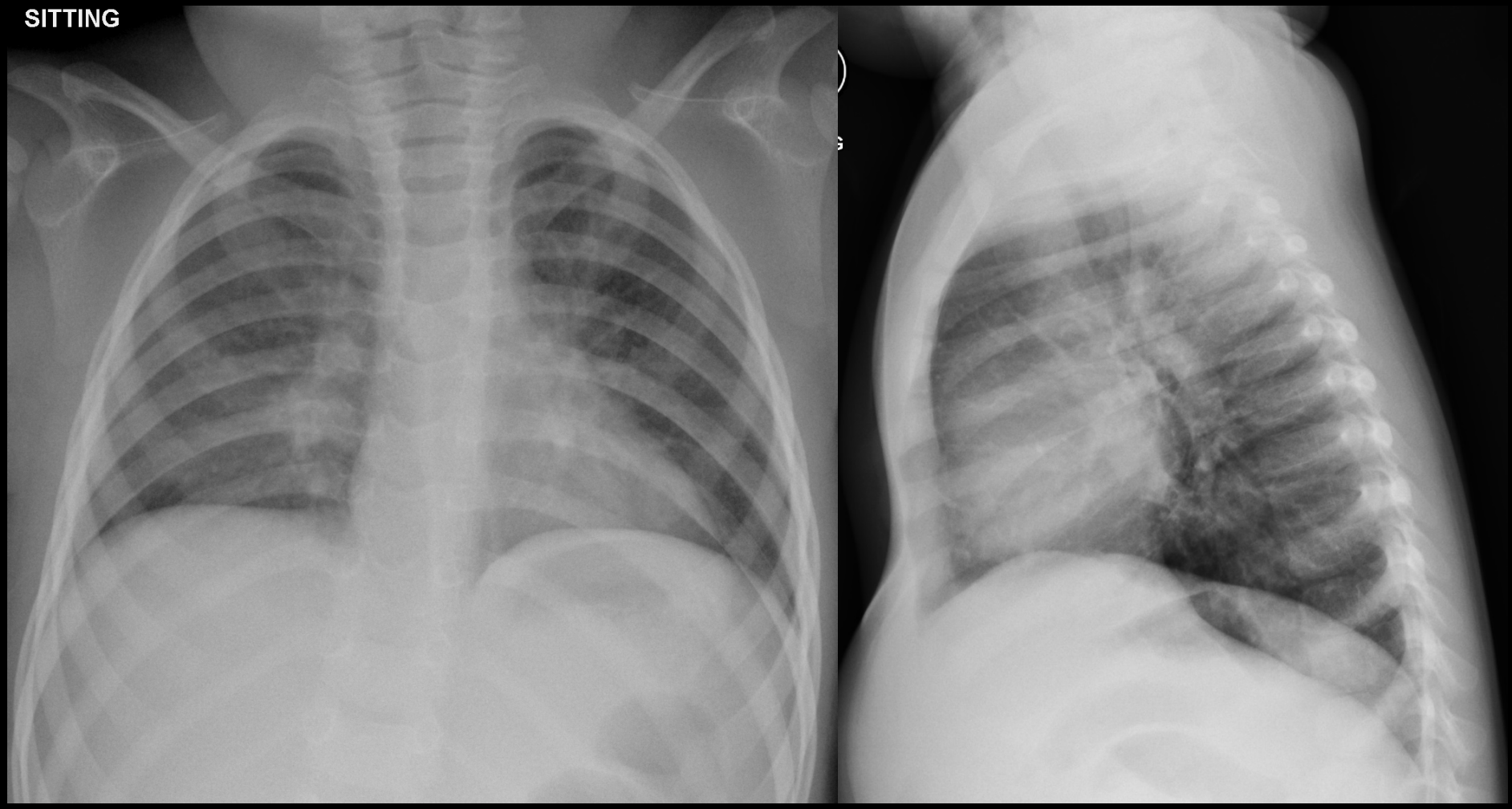
Case 3

- Clinicians decided to treat for TB on grounds of symptoms, positive TST and abnormal CXR
- 5 weeks later culture-positive, DST H and R resistant (katG mutation)
- Child recalled: gaining weight, clinically improved on HRZ
- What would you do now?

Case 3

- Took history again (aunt brought child). Again denied TB contact. Discovered mother in psychiatric unit because of “stress”. Why? Because her sister died previous year. Of what? TB! (this sister was child’s caregiver!). Looking on lab system – died of Pre-XDR-TB (H/R/O resistant)
- Also repeated CXR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Case 3

- Changed treatment regimen
- 4 active drugs:
  Am/Eto/Tzd/PAS/Cfz + Z (E? Lfx?)
- Clinically responded very well – consider giving only 15/12 of treatment
- Many social issues


Thank You!
Damien Schumann