Tuberculosis
in pediatric population

By

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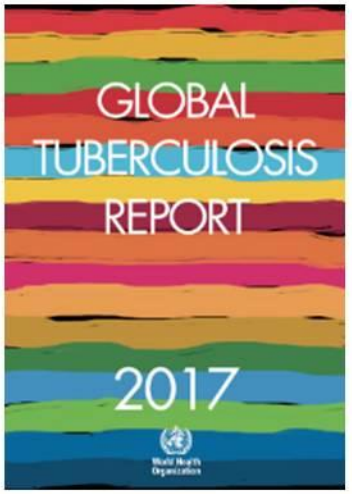
Scope

- **Management of childhood TB**
  - **Diagnosis of TB**
  - **Treatment TB in children**
- **LTBI**
- **The challenges**

TUBERCULOSIS

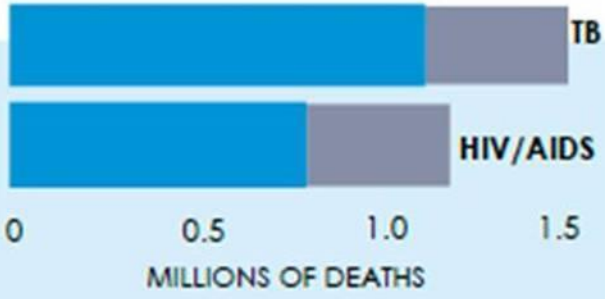
WHO Global Tuberculosis Report 2017



An estimated 10.4 million people fell ill with TB in 2016
An estimated 490 000 new cases of MDR-TB in 2016
9.7% of people with MDR-TB are estimated to have XDR-TB

47% drop in TB death rate
since 1990, with nearly all improvement since 2000

43 million lives saved
between 2000 and 2014 through effective diagnosis and treatment



TB ranks alongside HIV as a leading cause of death
with 1.5 million TB deaths in 2014*

10% of TB cases were children, 6.3% of new cases were <15 yo

http://www.who.int/tb/Global_TB

Criteria for Diagnosis of Childhood Tuberculosis

- **Clinical compatibility: Prolonged fever, weight loss, anorexia, anemia, prolonged cough > 2 weeks**
- **Hx of TB contact or Tuberculin skin test (TST) / IGRAs positive**
- **Chest X-rays compatible with TB**

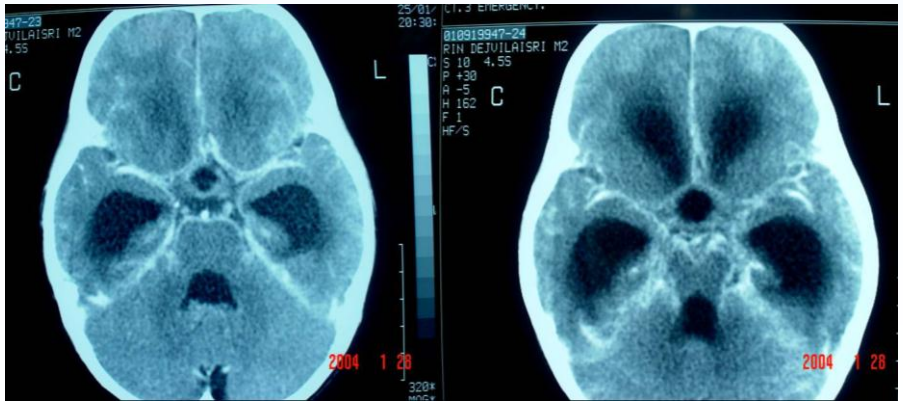
Diagnosis of TB could be difficult

due to non-specific presentations

Case 1: A 2 year-old boy with fever, cough, and rhinorrhea for 2 weeks

- 6 d PTA he developed seizure without meningeal sign. Dx febrile convulsion
- 4 d PTA he had high fever, lethargy and developed generalized seizure. PE : T 39º C, $E_1V_TM_5$, spasticity, + neck stiffness

- LP: P > 60/47 cmH_2O WBC 560 cells/mm^3 (L100%), protein 1,780 mg/dl, sugar 25/125 mg/dl

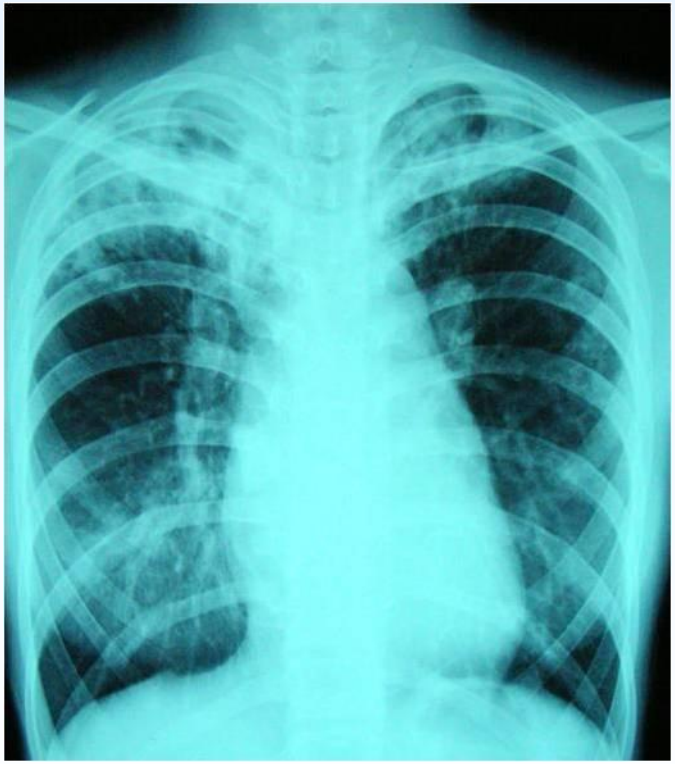


Case 1: Investigations

- **PPD skin test: negative**
- **Gastric wash AFB :**

  negative for 3 days
- **CSF PCR for TB: positive**
- **C/S for TB: no growth**
- **Anti-HIV: Negative**

Contact investigation for TB was performed



CXR of his mother

Management 1:
Diagnosis of TB requires high index of suspicion

- **Always think of TB if insidious onset and not improved by other treatments**
- **Persistent coughing >2 weeks**
- **Unresolving pneumonia**
- **Unexplained prolonged fever**
- **Unexplained weight loss despite nutritional Rx**
- **Unexplained lethargy**
- **For infants: hepatosplenomegaly, sepsis with insidious onset**
- **CNS involvement with hydrocephalus**

At Siriraj Hospital 2008-2011

- **TB was diagnosed in 230 children**
- **The median age was 6.5 years (4 d -17.5 years)**
- **HIV infection 9.6%**
- **Clinical presentation**
  - **Prolonged cough >14 days 32.2%**
  - **Prolonged fever >14 days 28.7%**
  - **Weight loss 15.2%**
  - **Asymptomatic 29.6% (with contact Hx 63.5%)**

Lapphra K . Int J Tuberc Lung Dis 2013;17:1279-84.

Approaches to Diagnosis of Childhood TB

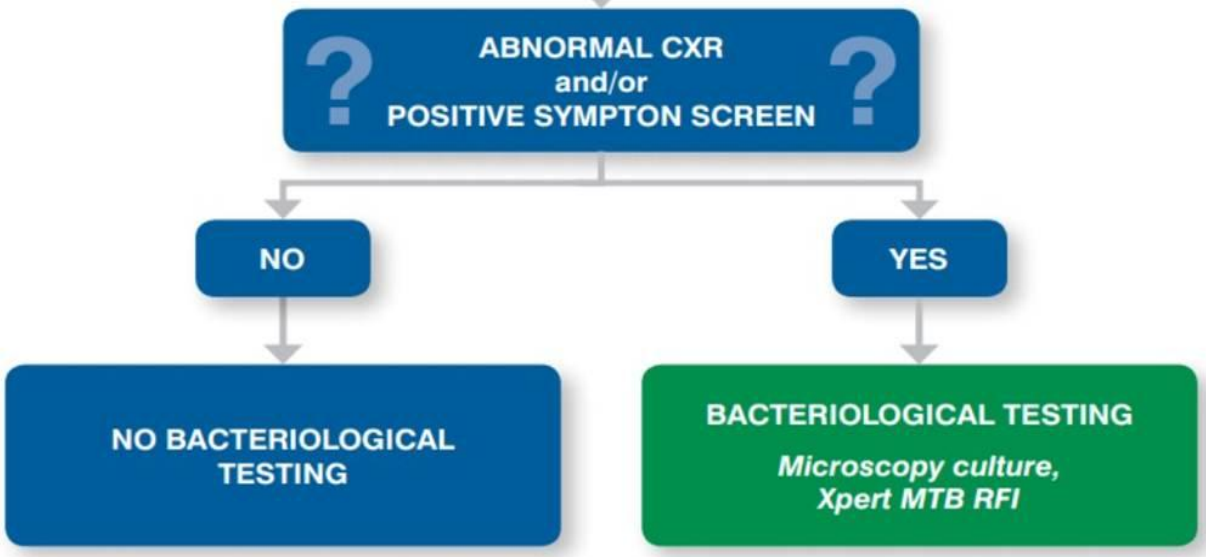
- **Careful history taking esp. history of TB contact in the last 24 months. High index of suspicion for extrapulmonary TB**
- **Careful physical examination including growth assessment**
- **Test for Immunological evidence of TB infection**
  - **TST ≥10 mm. (≥5 mm if HIV-infected, severe malnourished)**
  - **IGRAs (interferon-g release assays) in immunocompetent > 5 yo if available**
- **An HIV test (HIV-positive result should probably be treated as a proxy for TB)**
- **Bacteriological confirmation whenever possible**

TST and IGRAs in children < 5 years Siriraj Hospital

Test results	Total N=60	TB exposed N=43	TB disease N=17
TST			
Positive (%)	15 (25.0)	10 (23.3)	5 (29.4)
≥ 10 mm. (%)	15 (25.0)	10 (23.3)	5 (29.4)
≥ 15 mm. (%)	5 (8.3)	3 (7.0)	2 (11.8)
QFT-GIT			
Positive (%)	8 (13.3)	5 (11.6)	3 (17.6)
Indeterminate (%)	0 (0)	0 (0)	0 (0)
T-SPOT.TB.			
Positive (%)	12 (20.0)	8 (18.6)	4 (23.5)
Borderline (%)	2 (3.3)	1 (2.3)	1 (5.9)
Indeterminate (%)	2 (3.3)	1 (2.3)	1 (5.9)

CXR is Recommended for screening

FIG. 3. WHO's recommended screening strategy for TB prevalence surveys *(21)*



CXR: chest X-ray.

THE END TB STRATEGY

World Health Organization

- **23% and 70% of bacteriologically confirmed TB had chronic cough.**
- **Half will be missed by symptom screening alone**
- **To increase sensitivity, intentional overreading of CXRs should be encouraged**
- **Any abnormal CXR should get bacteriological examination, regardless of symptoms**
- **Immunocompromised person often shows atypical manifestations in a CXR**

Management 2:
Rapid drug susceptibility testing

- **Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources.**

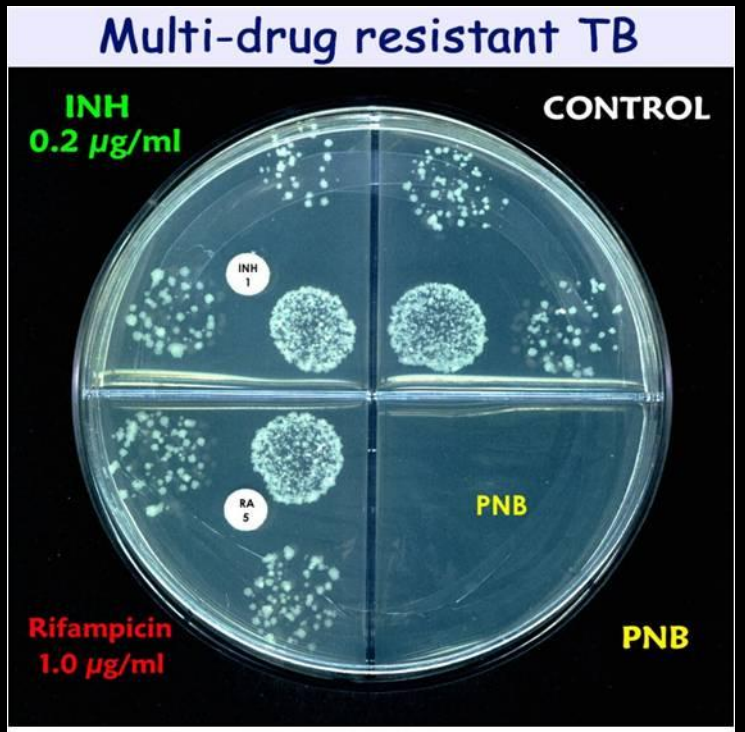
  (conditional recommendation, very low quality evidence).

2011 update of *Guidelines for the programmatic management of DRTB*

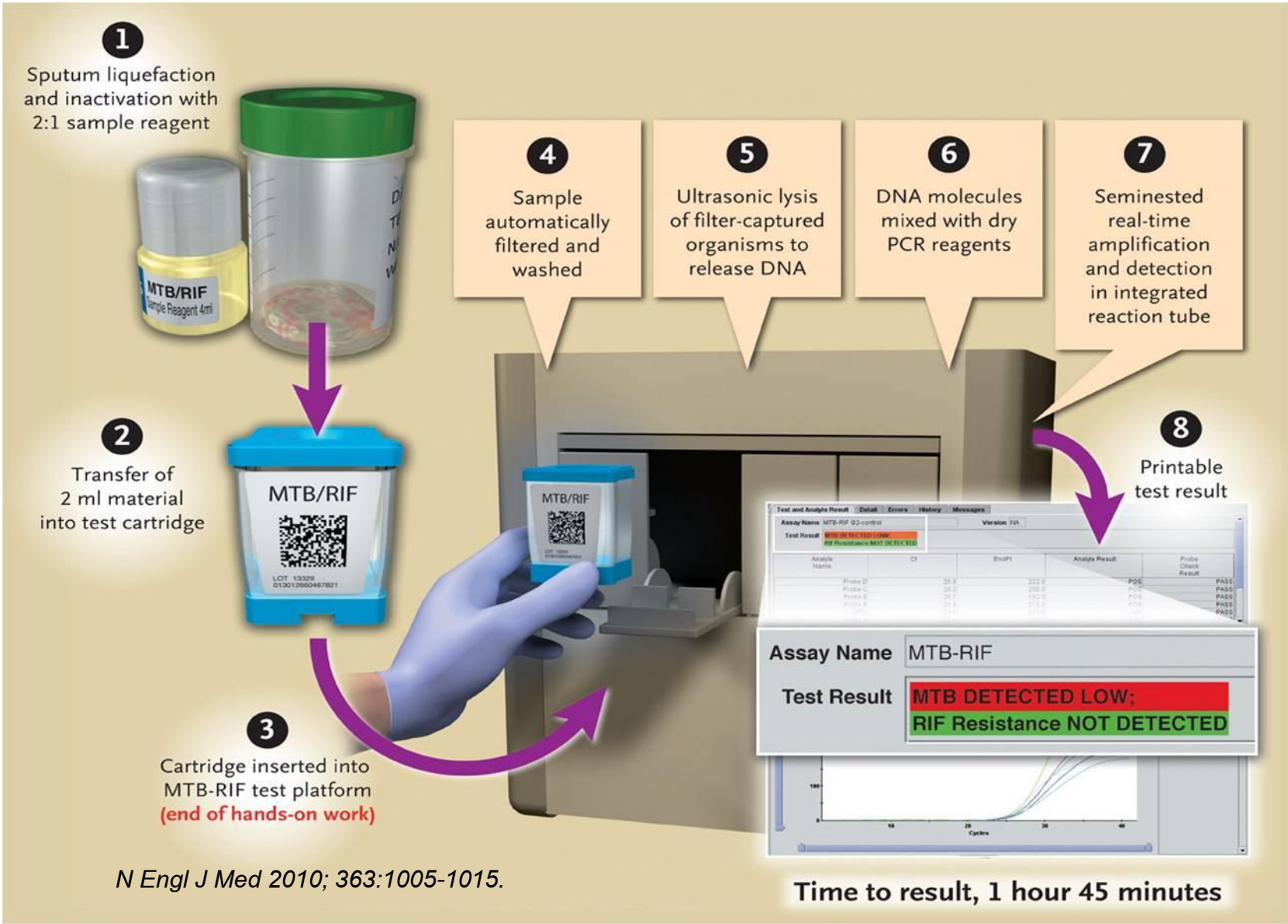
Conventional Test

- **Direct Susceptibility Test:**
  - Directly from clinical sample: Smear "positive"
  - M7H10 agar
  - Isoniazid and Rifampicin
  - Turnaround Time: 4 wks

- **Indirect Susceptibility Test:**
  - From pure culture
  - Turnaround Time: 4 weeks
  - M7H10 agar or LJ or MGIT

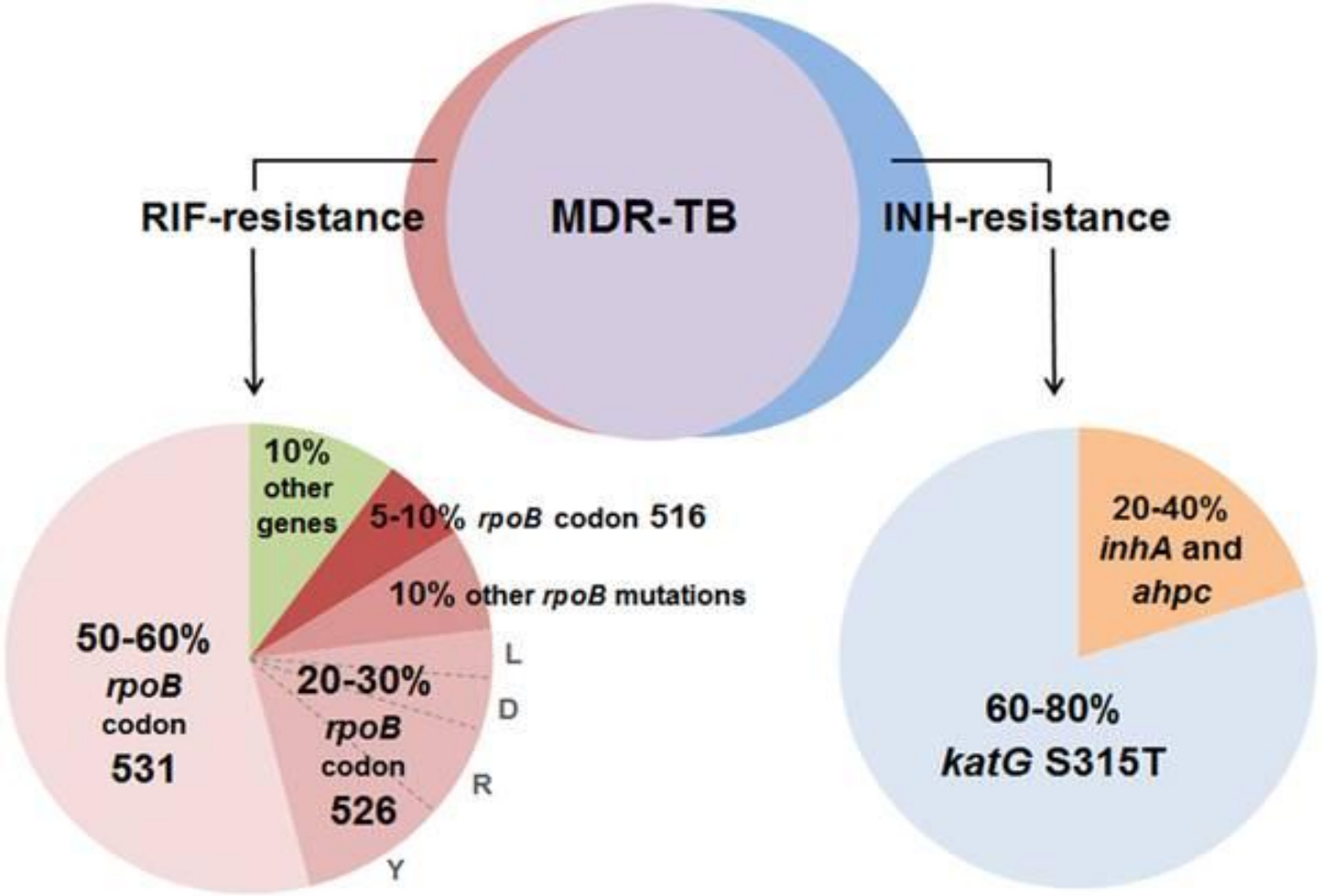


GeneXpert MTB/RIF



N Engl J Med 2010; 363:1005-1015.

Distribution of MDR-TB determining mutations



Rapid Molecular Detection of Multidrug-Resistant Tuberculosis by PCR-Nucleic Acid Lateral Flow Immunoassay

PLoS ONE 2015; 10(9): e0137791.

Line Probe Assay

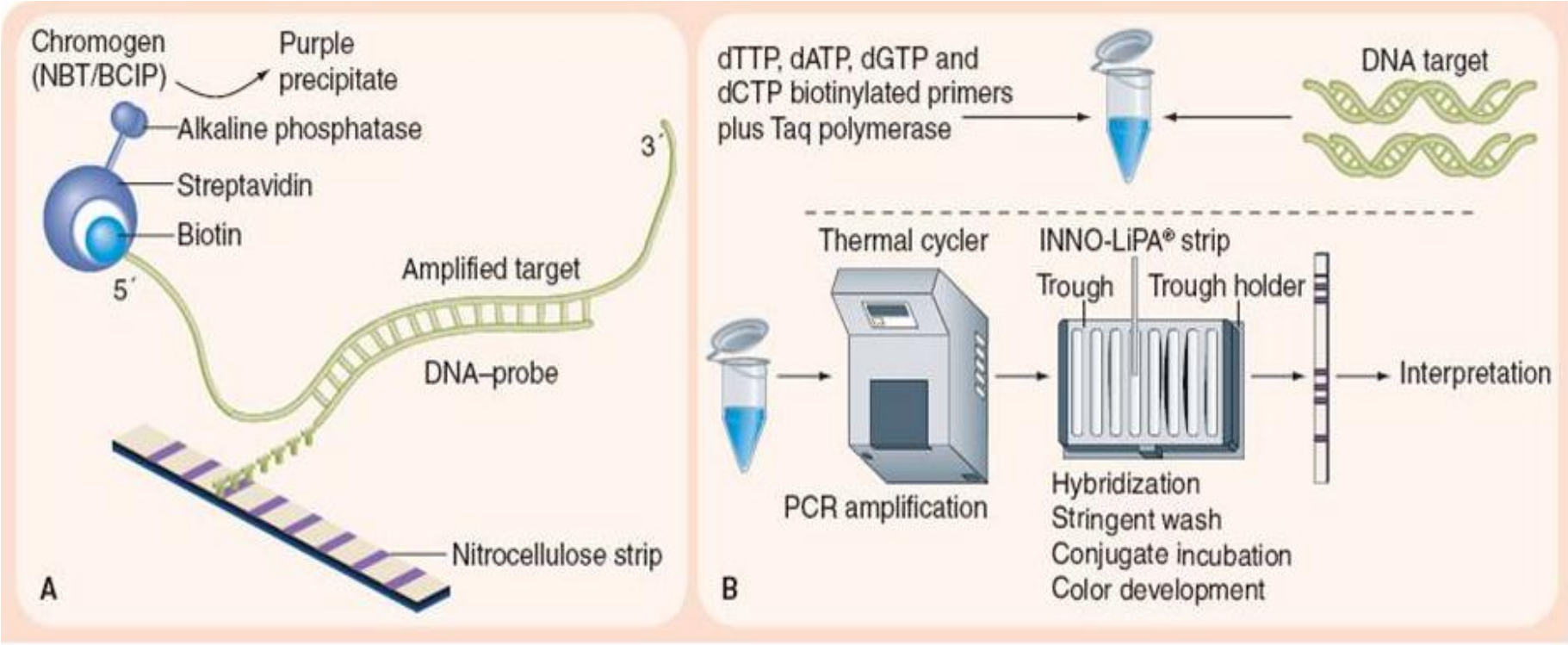


Figure 4. Line-probe assays for detection of drug resistance. **(A)** Principle of reverse hybridization. **(B)** INNO-LiPA® assay. The INNO-LiPA test contains ten oligonucleotide probes (one specific for the *Mycobacterium tuberculosis* complex, five overlapping wild-type S probes, and four R probes for detecting specific mutations) that are immobilized on nitrocellulose strips. LiPA is performed by extracting DNA and amplifying the rifampicin resistance-determining region of the *rpoB* gene using PCR. The PCR products are then hybridized with the immobilized probes, and results are determined by colorimetric development. Image adapted from Innogenetics NV (Gent, Belgium) © 2006 Innogenetics Group.

Management 3: Treatment in Children is not easy

- **No pediatric formulation in most anti-TB drugs**
- **Need DOT/adult supervision**
- **PK data recently available suggested that children have a lower exposure of anti-TB drugs compare to adults**

WHO Recommendation of Treatment of TB in Children 2010

- **Change dose recommended to avoid treatment failure while no evidence of increased hepatotoxicity (reported varied 1-80% incidence)**

  - INH : 10 MKD (10-15 MKD, max 300 mg/d)

  - RIF : 15 MKD (10-20 MKD, max 600 mg/d)

  - PZA : 35 MKD (30-40 MKD)

  - ETB : 20 MKD (15-25 MKD) >>> *unchanged*
- ***Avoid streptomycin as the first line***
- **Use IRZE in intensive phase for all except in not extensive lesion in area with low HIV and low INH-resistance that can use 3 drug IRZ**

  (Strong recommendation, moderate quality evidence)

Regimens for Rx tuberculosis

Tuberculosis	Regimens
Pulmonary TB	2 IRZE/4 IR
TB osteomyelitis, TB meningitis, Disseminated TB	2 IRZE/10 IR
MDR-TB	At least 4 active drugs Fluoroquinolone+ Aminoglycoside 2nd line: Ethio/Cycloserine/PAS Bedaquiline/Delamanid

Prednisolone 4 - 8 wk in TB meningitis, paradoxical reaction (Miliary TB 30% had CNS involvement)

WHO Recommendation 2010

Not recommend twice weekly, but trice-weekly continuation phase may be considered in HIV-uninfected children with well-established DOT *(Weak recommendation, very low quality evidence)*

Author	Dose/wk	N	Cure rate Intermittent VS Daily
Kumar 1990	twice	76	93% VS 100%
Te Water 2000	twice	213	89% VS 97%
Al-Dossary 2002	Twice from wk3	185	37%
Ramachancran 1998	Twice wk 1-8 IRZ then twice IRZ (Daily only IR)	141	48% VS 60%

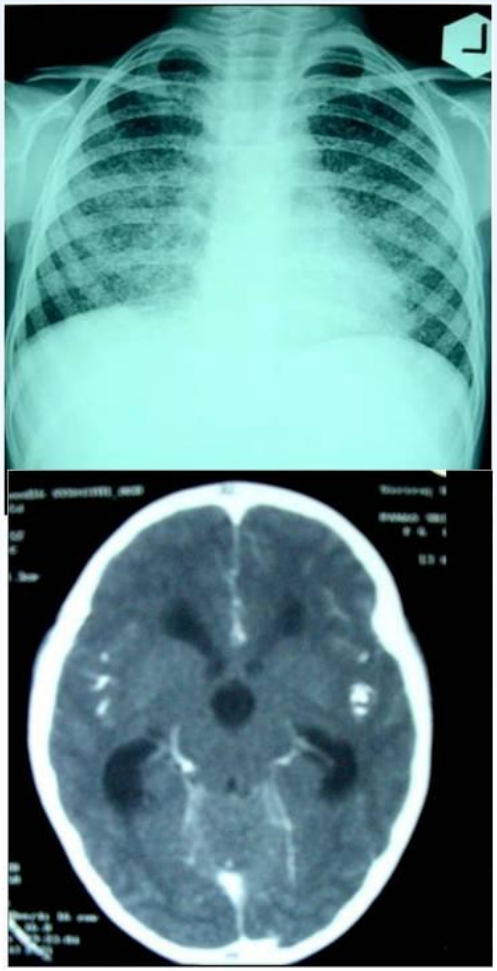
Menon et al. (meta analysis): twice/wk less likely to cure (PP or 0.27 95% CI 0.15-0.51 ITT or 0.66, 95% CI 0.23-1.84)

Case : An 18 month-old with miliary TB

- **18 month old girl with prolonged fever and chronic cough. CXR found miliary TB. IRZS was started.**

- **4 weeks later, she had weakness of left leg with long track sign, hyper-reflexia.**

  CSF wbc = 350 (L90%), sugar was 30 mg%, protein was 250 mg%



The CNS symptoms may be presented after Rx initiation.

Treat Miliary TB as CNS TB

- **For miliary TB, look for CNS involvement. LP should be done**

  - 75% (12/16) of patients with miliary TB had CNS involvement identified by MRI. Of these, only half had symptoms… *Sasaki Y. Kekkaku 2000;75:423-7.*

  - 20-30% of patients with CNS TB had miliary TB… *Yamaris A. Pediatrics 1998;102: E49., van den Bos F. Trop Med Int Health 2004;9:309-13.*

Prevalence, Characteristics, Management, and Outcome of Pulmonary Tuberculosis in HIV-Infected Children in the TREAT Asia Pediatric HIV Observational Database (TApHOD)

- **457/ 2678 HIV-infected children developed PTB over a 13-year period; prevalence of 17.1% (range 5.7-33.0% per country).**
- **There were 21 deaths (4.3%).**
- **One third of episodes (n=175/484) occurred after ART initiation at a median of 14.1 months**
- **After Rx, 81.9% had good outcomes**

AIDS PATIENT CARE and STDs 2013;27:649-56.

Management 4 : Drug resistance in childhood TB is rising, shadowing what seen in adults

Case: A 2 month-old male infant with hydrocephalus

- **He was well looking and sent to Siriraj Hosp. for evaluated the cause of hydrocephalus.**
- **CSF : WBC 12 cells/mm^3**

  (L76%, Mono 23%)

  protein 82 mg/dl, sugar 29 mg/dl

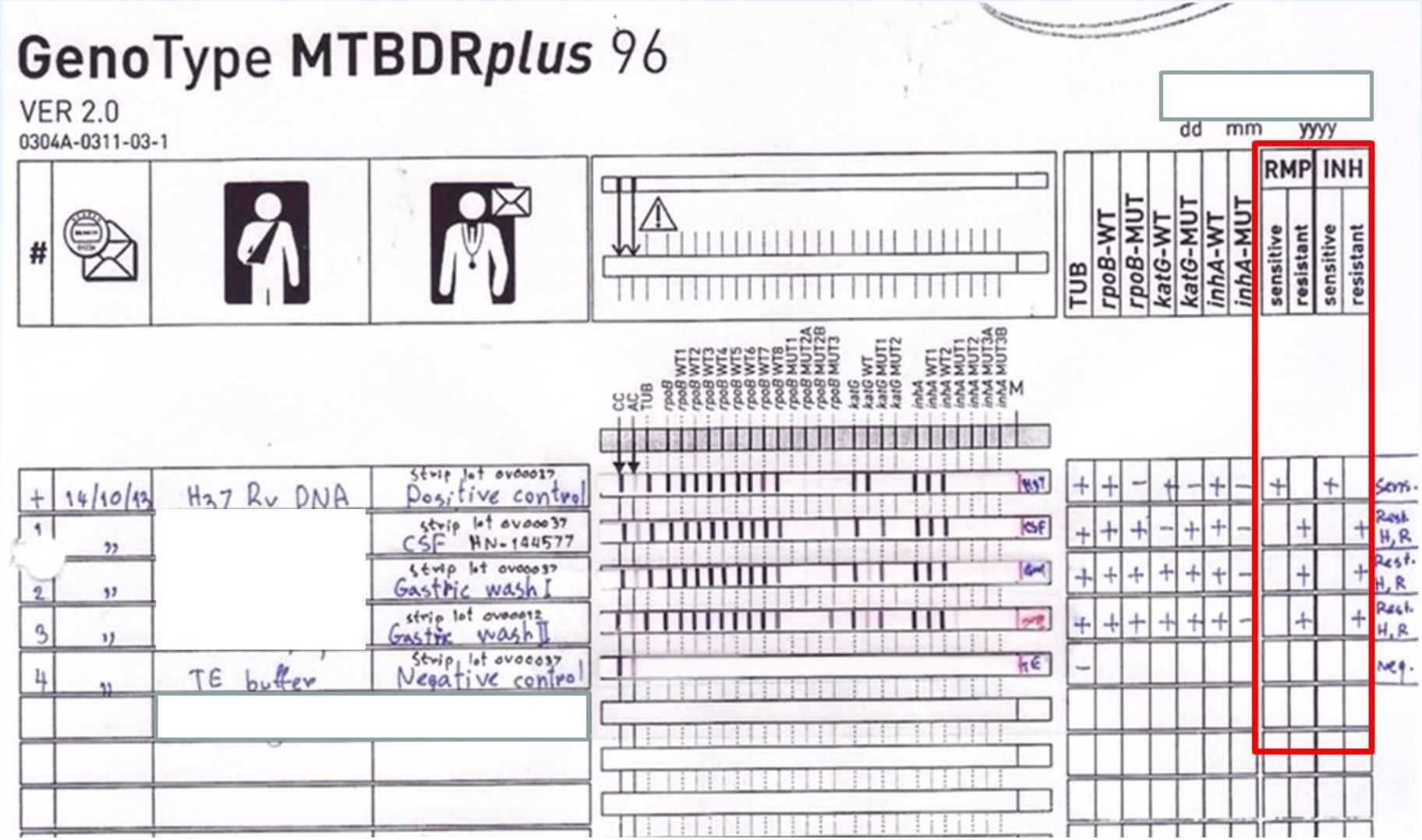
  C/S no growth, AFB –ve,

  PCR TB +ve
- Gastric aspirate: AFB –ve x 3 days

  PCR TB +ve
- **Contact Inx in family: CXR**

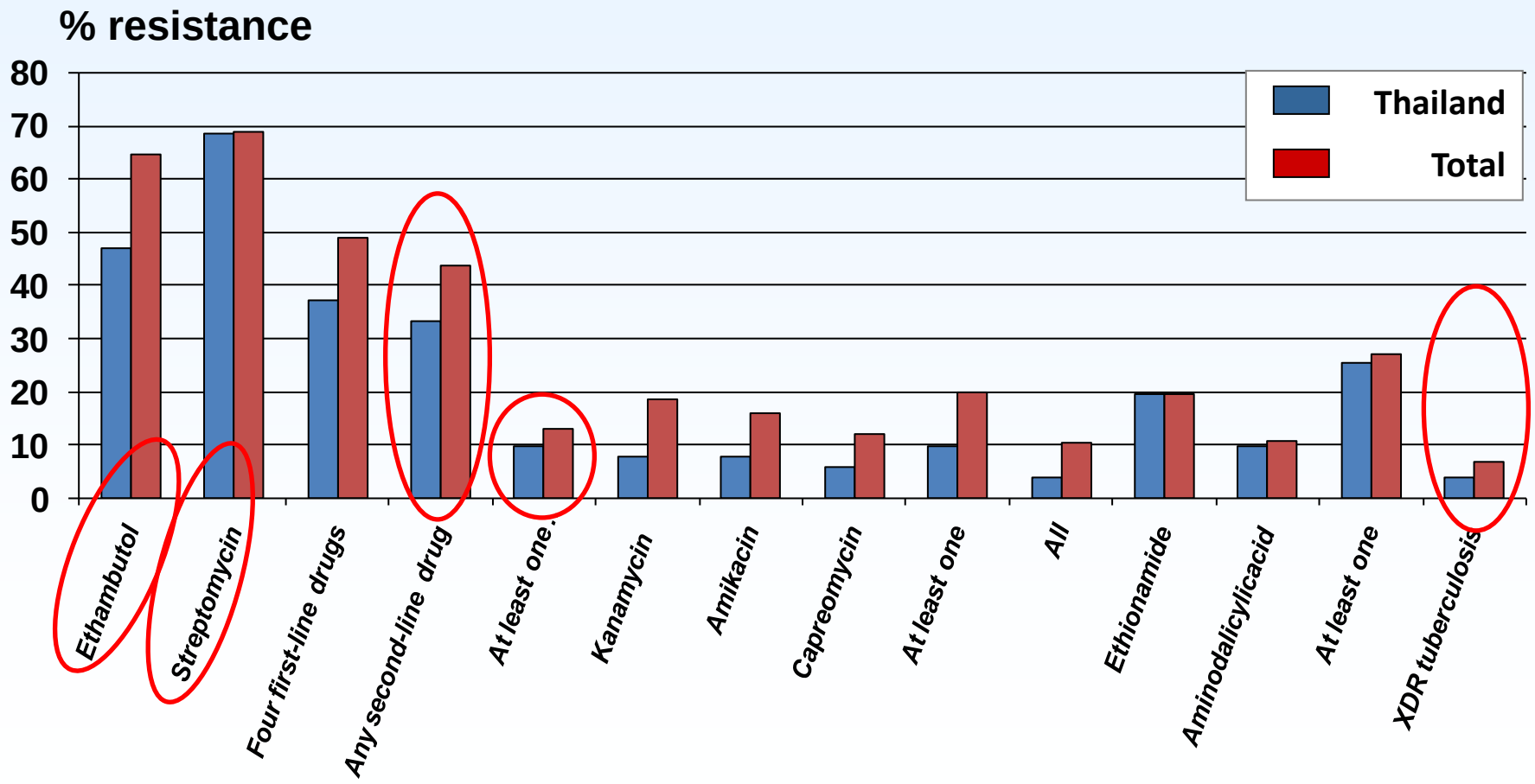
  6 people negative

MDR TB meningitis with pulmonary MDR TB



Prevalence of and risk factors for resistance to second-line drugs in people with MDR TB in 8 countries: a prospective cohort study

Previous treatment with 2nd line drugs associated with resistance to the drugs



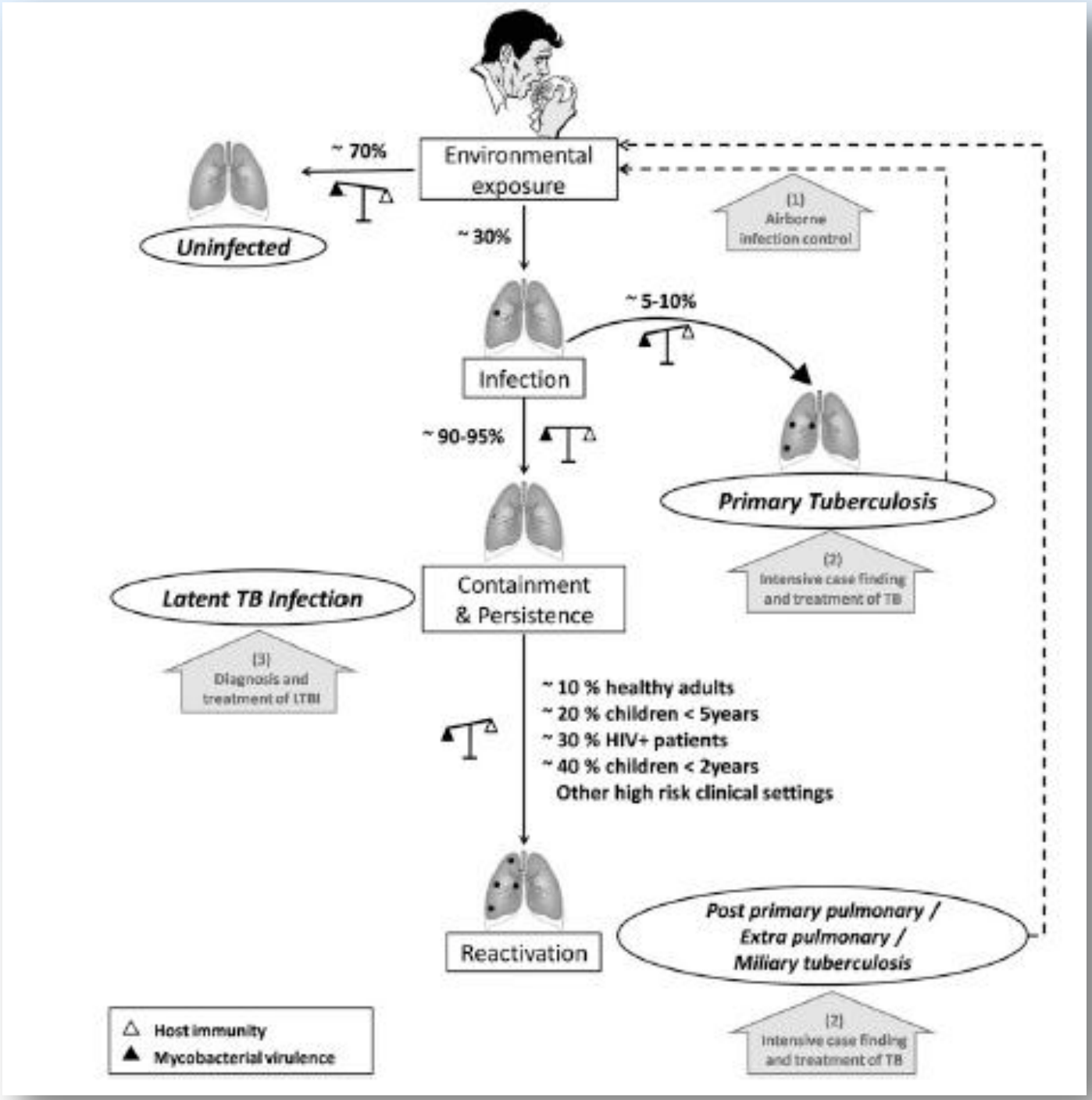
Dalton T. The Lancet 2012.

Management 5: Control of Childhood TB

The best control of childhood TB is to treat active adult case early and perform contact investigation in children

Don’t forget to check out household members

TB of Spine: Contact with father who had TB 3 years earlier but never been told to bring the child in for check -up



1/3 of the World population is believed to have LTBI

Chest 2012;142:761-773.

Latent Tuberculosis

- **The condition that infection is established, but disease has not occurred**
- **Mostly diagnosed by reactive TST or IGRA in asymptomatic individuals**

- **It is the quiet period which may progress to TB or resolution of the infection**
- **It is the window of opportunity to prevent TB development**

Risk factors for the development of active TB among persons infected with *M. tuberculosis*

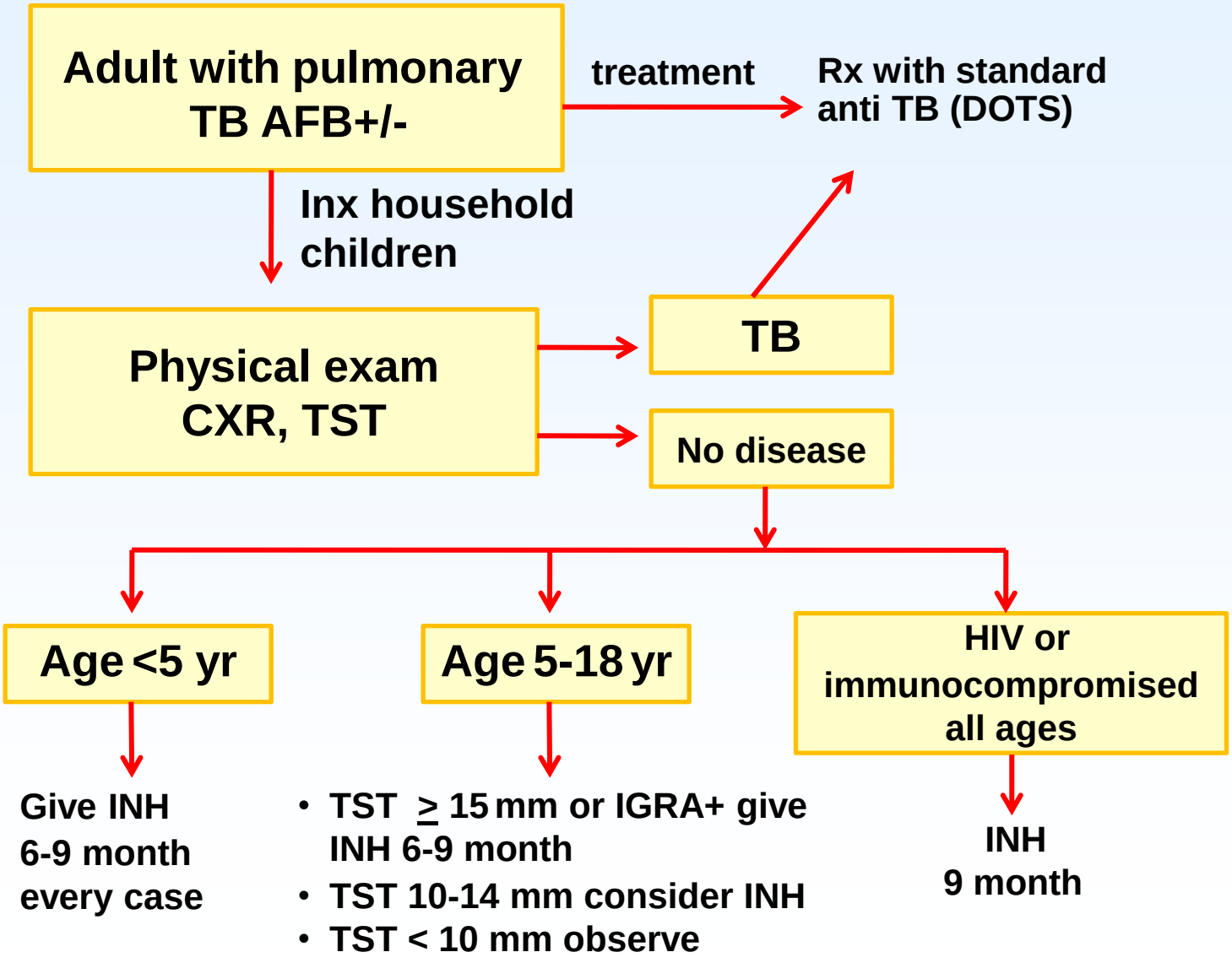
Risk factor	Estimated risk for TB relative to persons with no known risk factor
High risk (testing and treatment for LTBI recommended for all ages)	
AIDS (not on anti-HIV therapy)	110–170
HIV (not on anti-HIV therapy)	50–110
Transplantation (related to immunosuppressive therapy)	20–74
Silicosis	30
Chronic renal failure requiring hemodialysis	10–25
Carcinoma of head and neck	16
Recent TB infection (<2 yrs)	15
Abnormal chest X ray—with upper lobe fibronodular disease typical of healed TB infection	6–19
TNF-α inhibitors	2–9
Moderate risk (testing and treatment for LTBI recommended if age < 65 yrs)	
Treatment with glucocorticoids	5
Diabetes mellitus (all types)	2–4
Young age when infected (0–4 yrs)	2–5
Slightly increased risk (testing and treatment for LTBI recommended if age < 50 yrs)	
Underweight (<90% ideal body weight; for most persons, this is a BMI of 20)	2–3
Cigarette smoker (1 pack/day)	2–3
Abnormal chest X ray—granuloma	2
Low risk (testing and treatment for LTBI recommended if age < 35 yrs)	
Infected person, no known risk factor, normal chest X ray ("low-risk reactor")	1
Very low risk (treatment of LTBI not usually recommended)	
Person with positive two-step ("boosting"), no other known risk factor, and normal chest X ray	0.5

[a]Modified from the work of Lobue and Menzies (140) and the CDC.

Haley CA. ASMscience.org/MicrobiolSpectrum 2017.

Respirology 2010;15:603–622. Semin Respir Crit Care Med 2013; 34:67–86.

Contact investigation and Management



Regimens Used for LTBI treatment

Regimen	Efficacy	Adherence	Incidence of drug-induced hepatitis
Daily H 6 mo	69%	50%	1-5%
Daily H 9-12 mo	90-93%	< 50%	1-5%
Daily RH 3-4 mo	~ 6 mo H	Slightly better (by6%) than 9-12 mo H	1-5%
Daily RZ 2 mo	~ 9-12 mo H	Slightly better (by6%) than 9-12 mo H	3-5%
Daily R 3-4 mo	65%	Much better (by 22%) than 9-12 mo H	<1%
Twice-weekly RH 3 mo	~ 6 mo H	95%	2.4%
Weekly RH 3 mo	~ 9 mo H	82-96%	0.4-1.5%

Chest 2012;142:761-773.

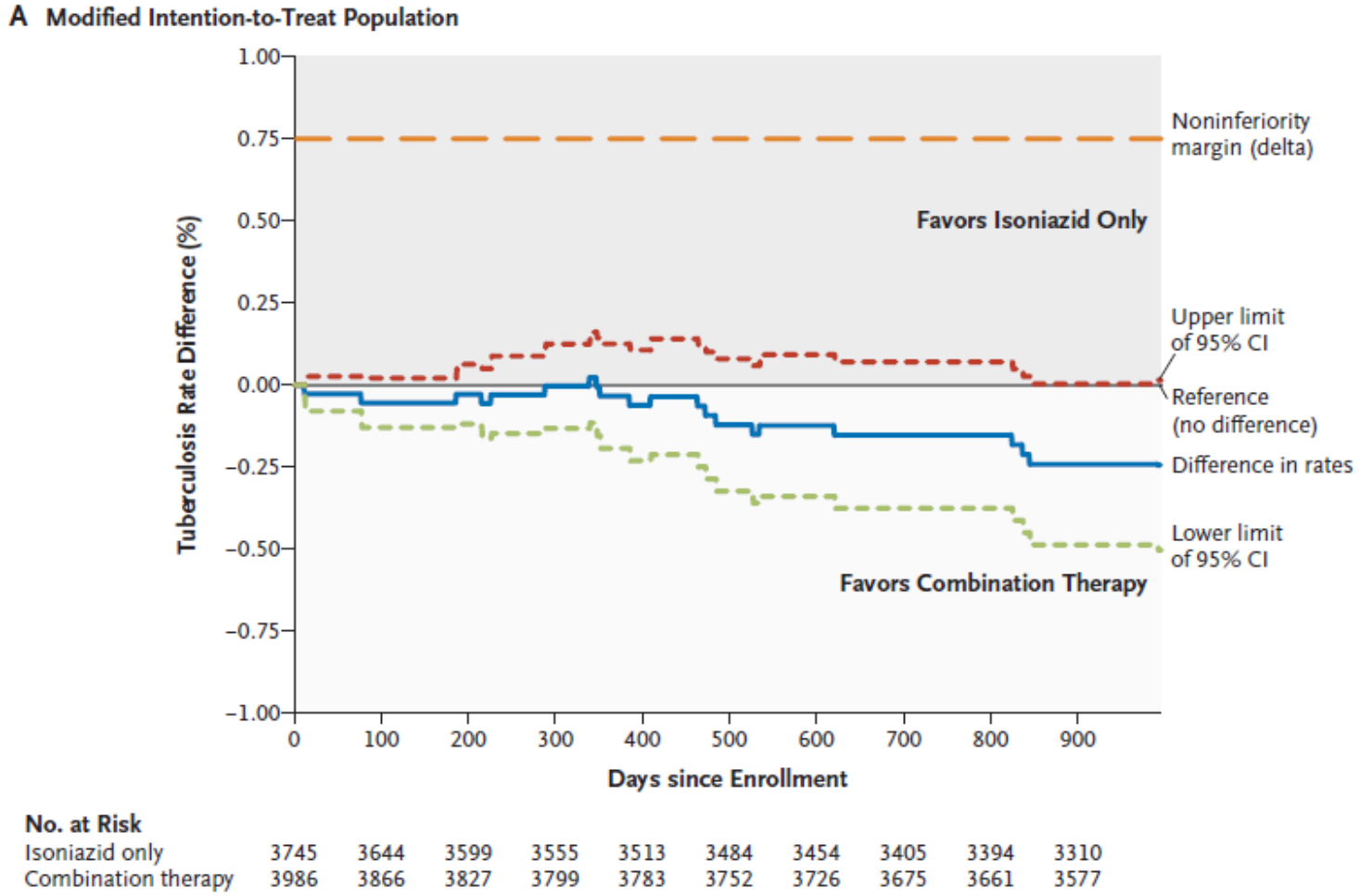
30 Years Study Confirmed INH prophylaxis works in Children and Adolescents

Need to put INH prophylaxis in TB-exposed/LTBI in children. Not too early, but not too late

	Rate TB(/1,000) in INH Rx vs no Rx
At 20 yr. report	4.2 vs 10.1
At 30 yr. report (for <3 yo.)	0.5 vs 7.5

Katharine H. K. Hsu. JAMA 1984;251:1283-5.

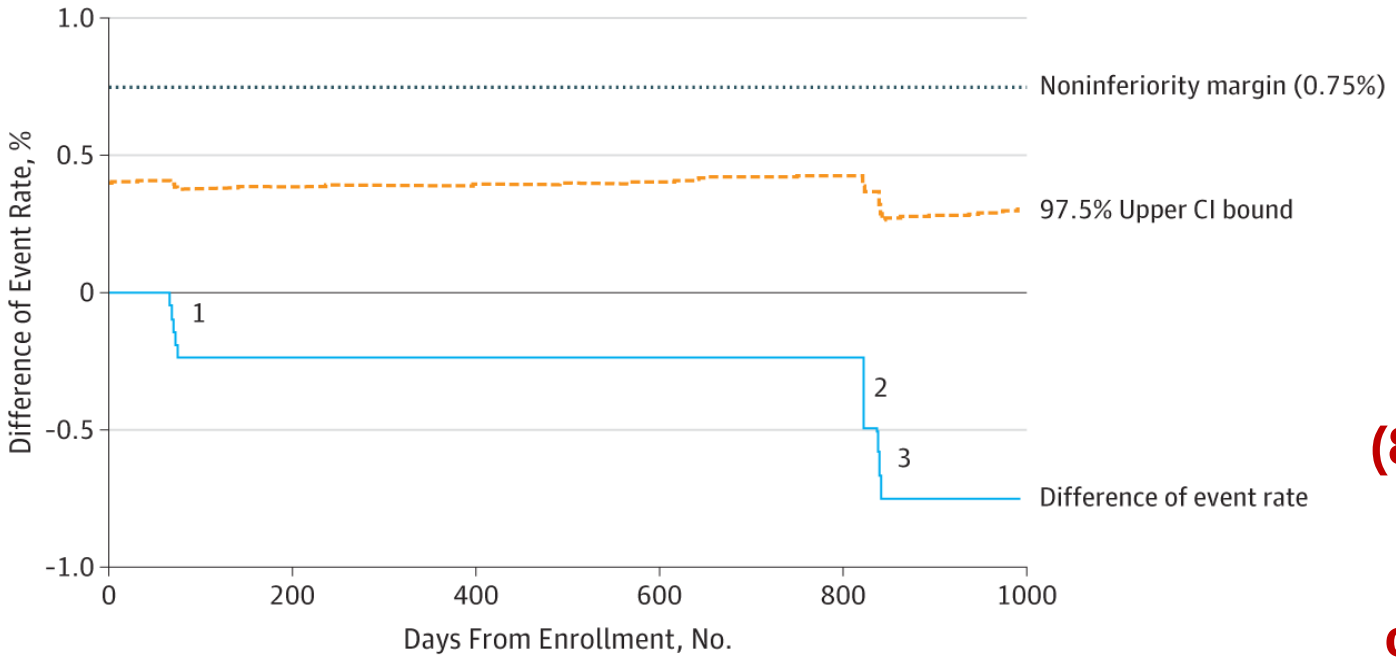
Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection



Rifapentine + INH for 3 mo was as effective as 9 mo of INH alone in preventing TB and had a higher treatment-completion rate

Sterling TR. N Engl J Med 2011;365:2155-66.

Treatment for preventing tuberculosis in children and adolescents: RCT of a 3-month, 12-dose regimen of a combination of rifapentine and INH vs INH alone



12 dose combo had higher completion rate (88% VS 81%) with similar AE compared to INH alone

No. of TB Cases and Event Rates by Treatment Arm (MITT Population)

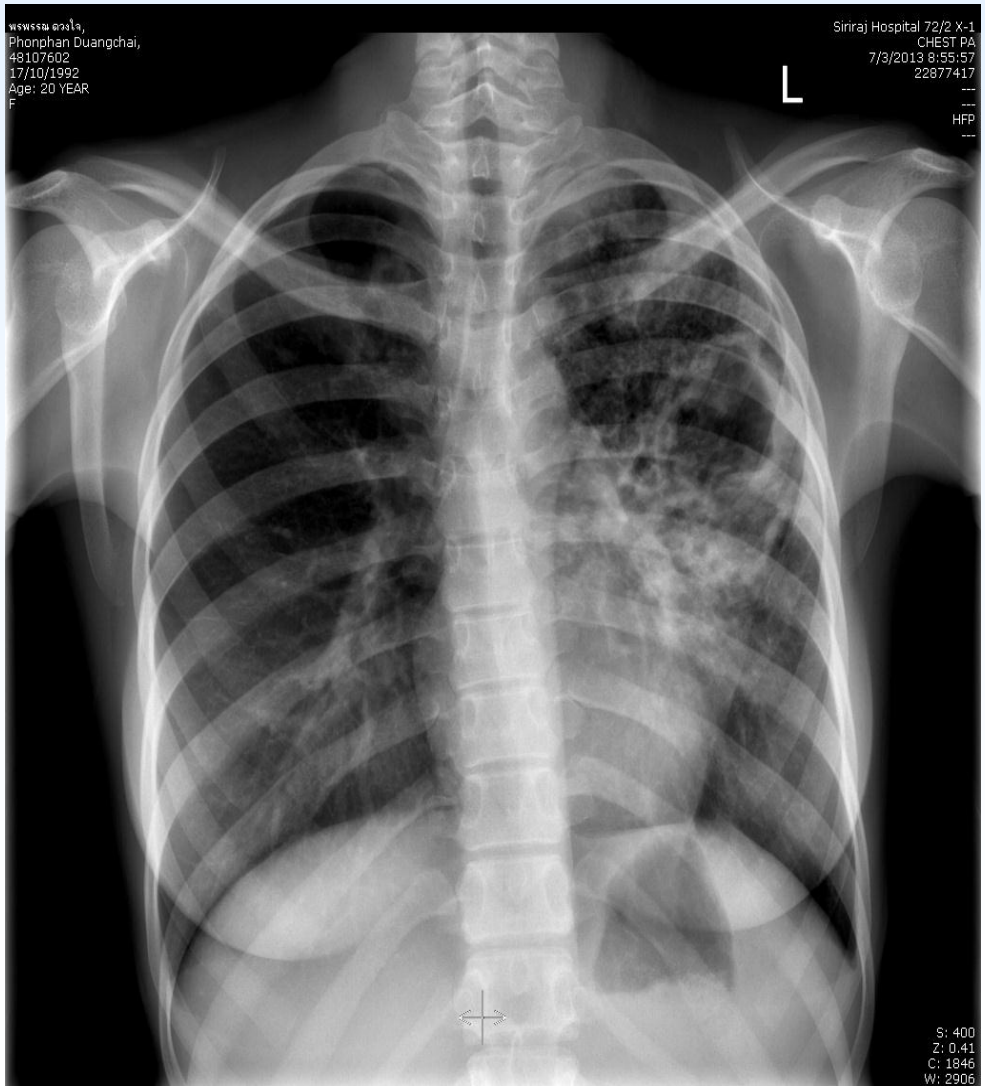
Treatment Arm	No.	TB Cases[a]	TB per 100 Patient-Years	Cumulative TB Rate, %	Difference in Cumulative TB Rates	One-sided 97.5% CI[b]
Isoniazid only	434	3	0.27	0.74	-0.74	0.32
Combination drug therapy	471	0	0.00	0.00		

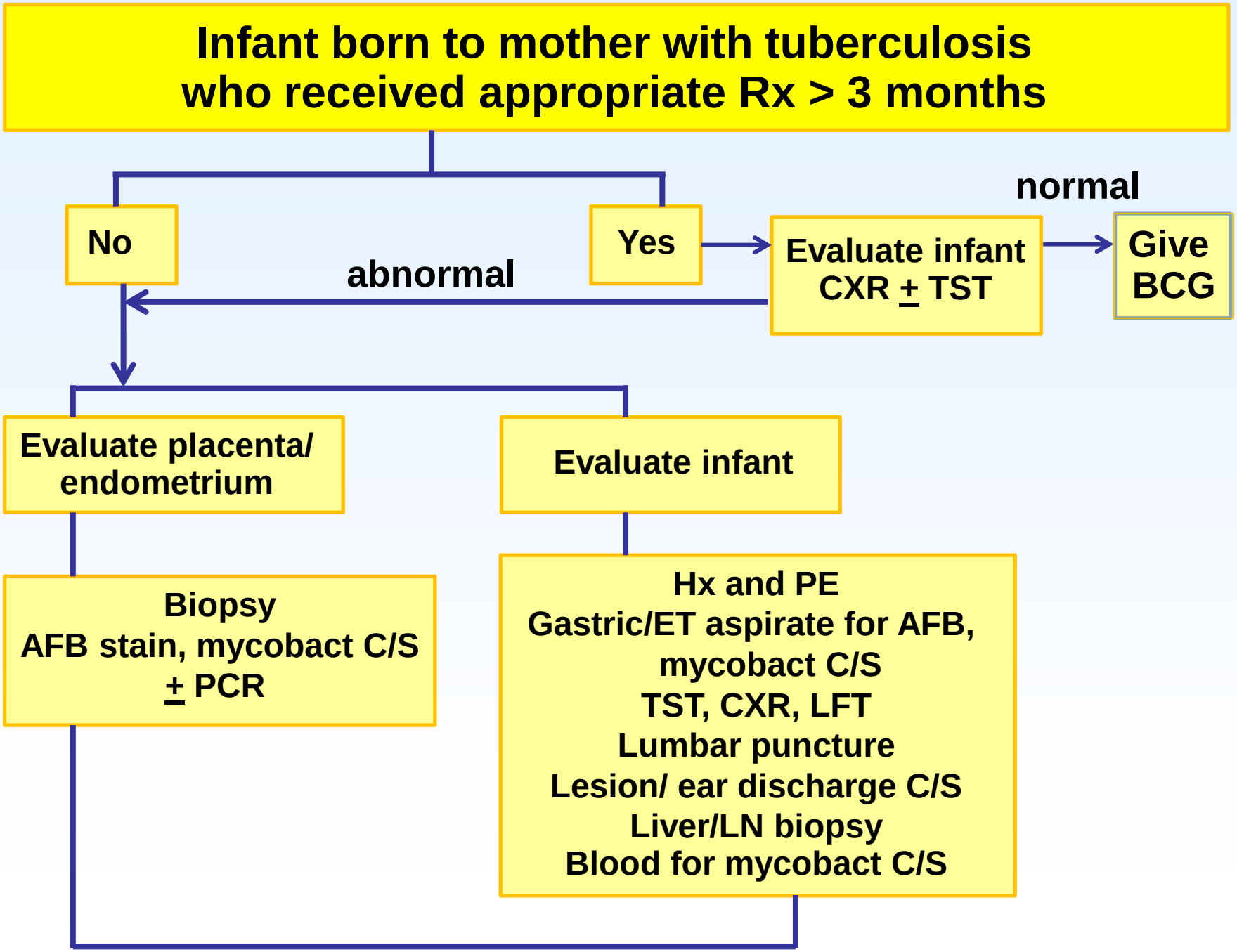
Q wk by DOT

Villarino ME. JAMA Pediatr 2015;169(3):247-55.

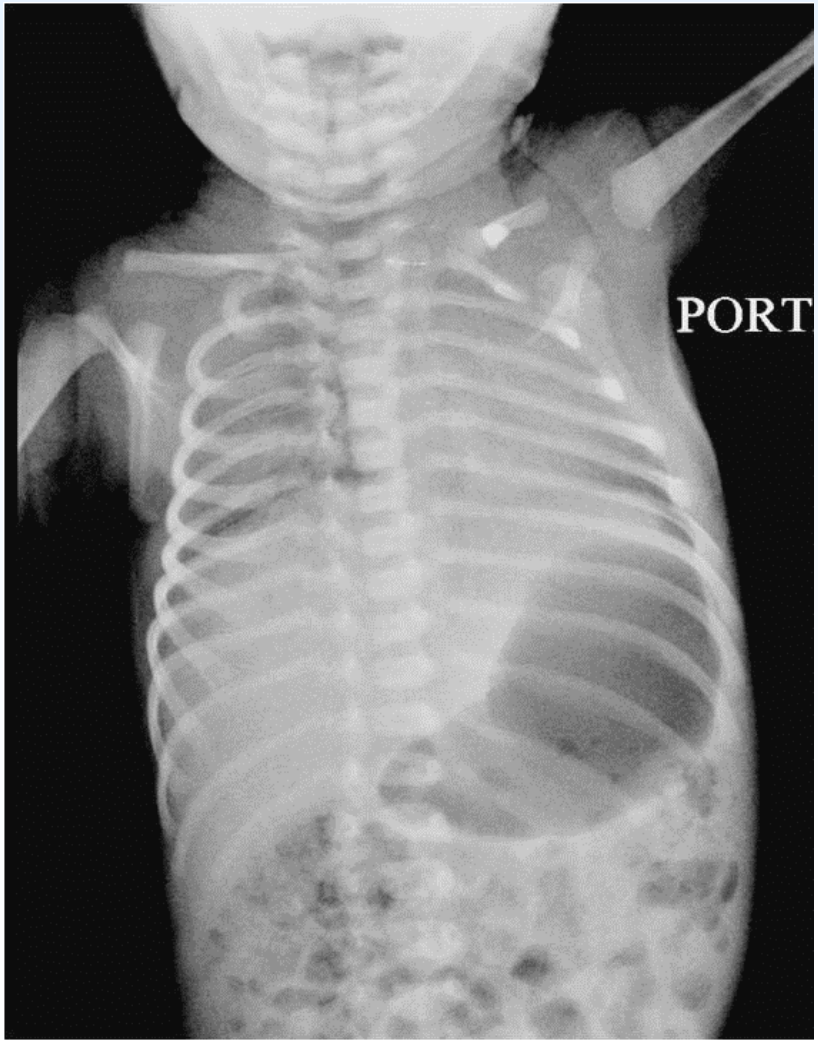
Newborn contact maternal TB

- Mother 21 yr. $G_2P_1A_0$ GA 38 wk ANC x11 times, serology negative all
- Hx of chronic cough 8 months before delivery, no fever, No TB in her family
- CXR
- Sputum : AFB 2+
  - Direct PCR : + TB complex
  - C/S: *M.tuberculosis* complex
  - Direct PCR : no mutation in *rpoB* gene, *katG* gene, *inhA* gene




Infant born to mother with tuberculosis
who received appropriate Rx > 3 months
No
Yes
normal
abnormal
Evaluate infant
CXR ± TST
Give
BCG
Evaluate placenta/
endometrium
Evaluate infant
Biopsy
AFB stain, mycobact C/S
± PCR
Hx and PE
Gastric/ET aspirate for AFB,
mycobact C/S
TST, CXR, LFT
Lumbar puncture
Lesion/ ear discharge C/S
Liver/LN biopsy
Blood for mycobact C/S

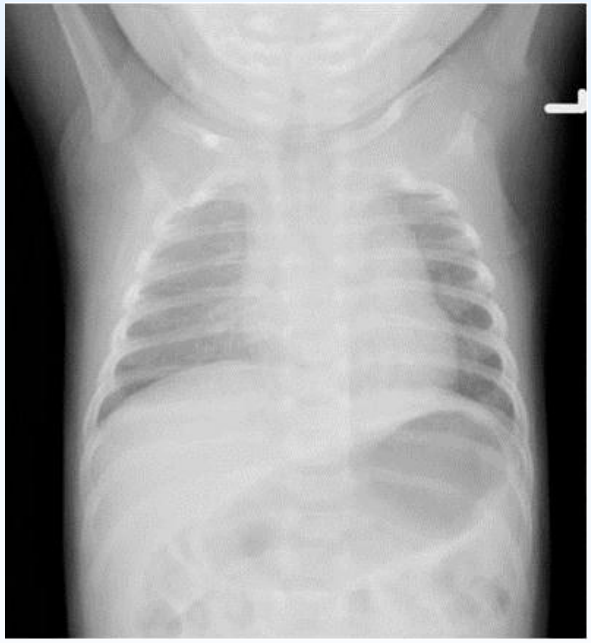
Newborn contact maternal TB



- **CBC: Hb 15.8 g/dl, Hct 46.3%, WBC 10,000/ul (N 51.3%, L 35.3%, Mo 7.3%, Eo 5.9%), Plt 143,000/ul**
- **CSF: WBC 1 , RBC 3, protein 114, sugar 59/blood sugar 111**
- **CSF : AFB neg., PCR-TB neg, C/S no growth for bacteria**
- **Gastric wash x 3 days: AFB neg, PCR-TB neg, c/s neg**

Newborn contact maternal TB

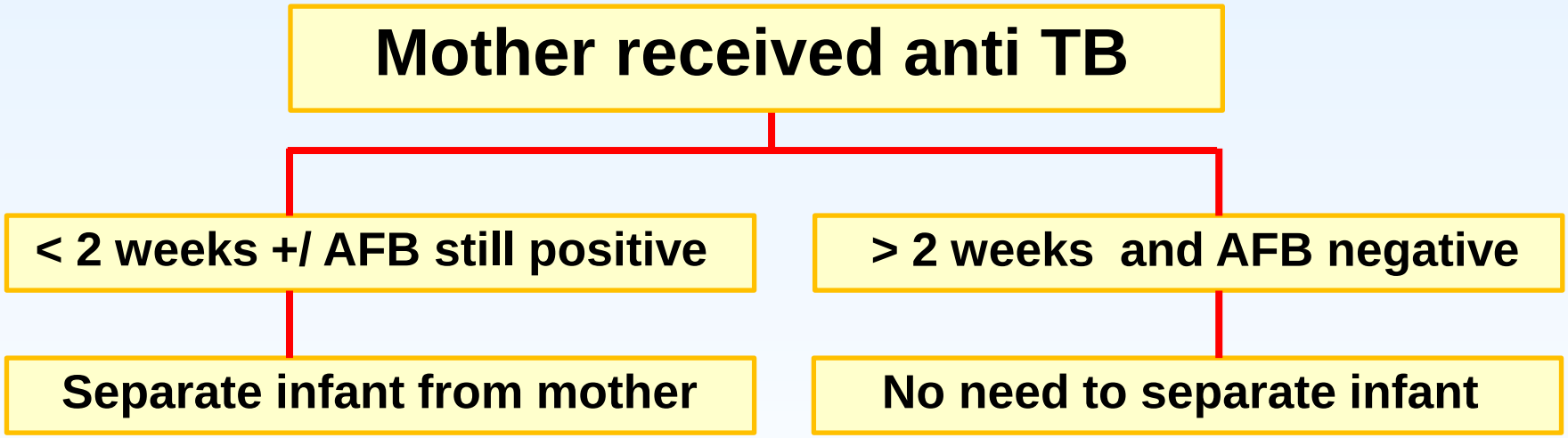
- **Rx congenital pneumonia**
  - **Ampicilline + gentamicin x 7 days**



CXR F/U after Rx pneumonia

Contact TB: Isoniazid prophylaxis 9 months

Infant born to mother with pulmonary TB



Not considered a contra-indication to breastfeeding
TB drugs don't harm the neonate

Give vitamin B6 0.2-0.5 mg/day in infant who receiving INH

The Challenges

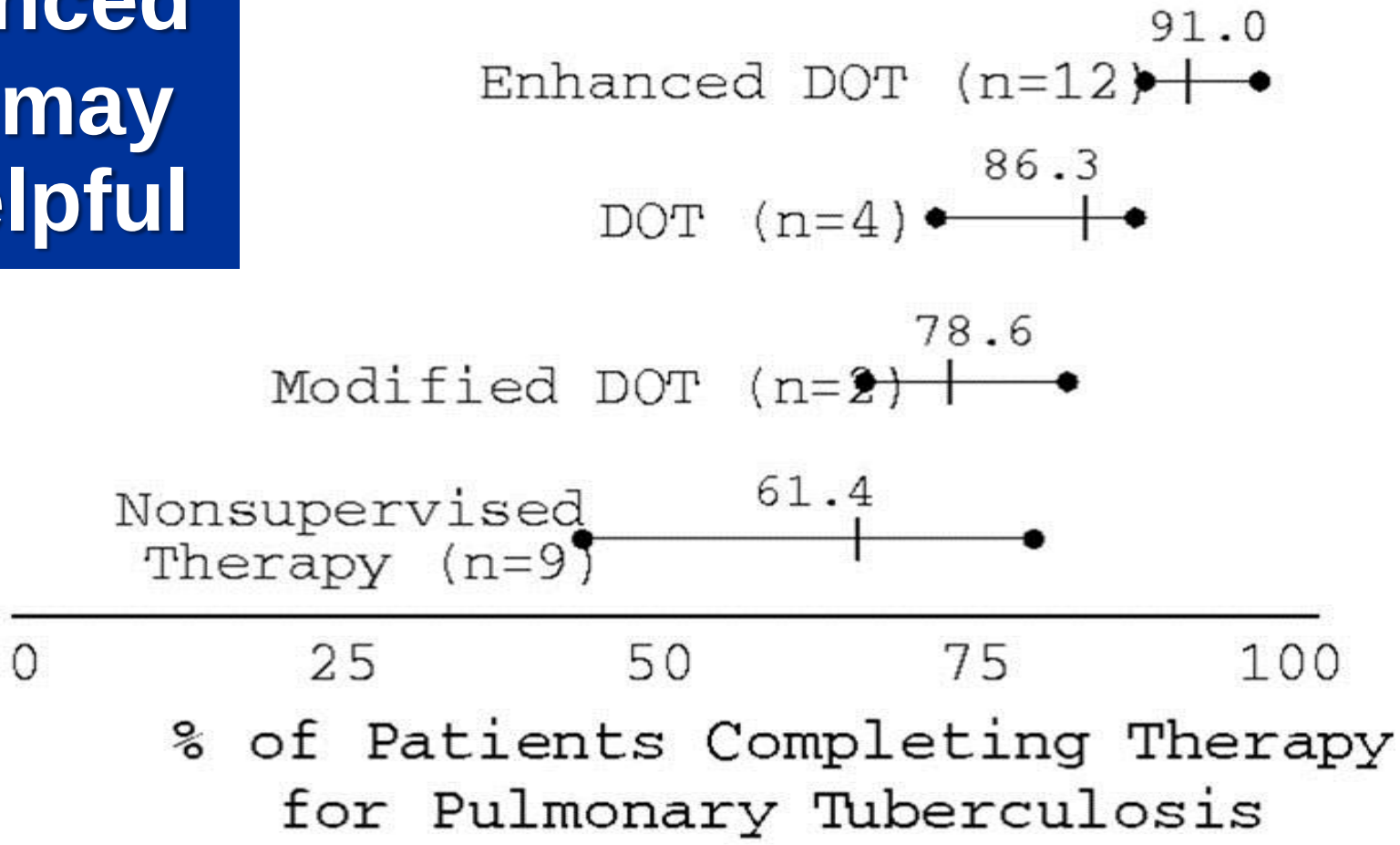
Challenges

Meds in 1 day

Cycloserine (+B6), PAS, Ethionamide, Levoflox
+ amikacin IV OD

Directly observe therapy (DOT)

Enhanced DOT may be helpful



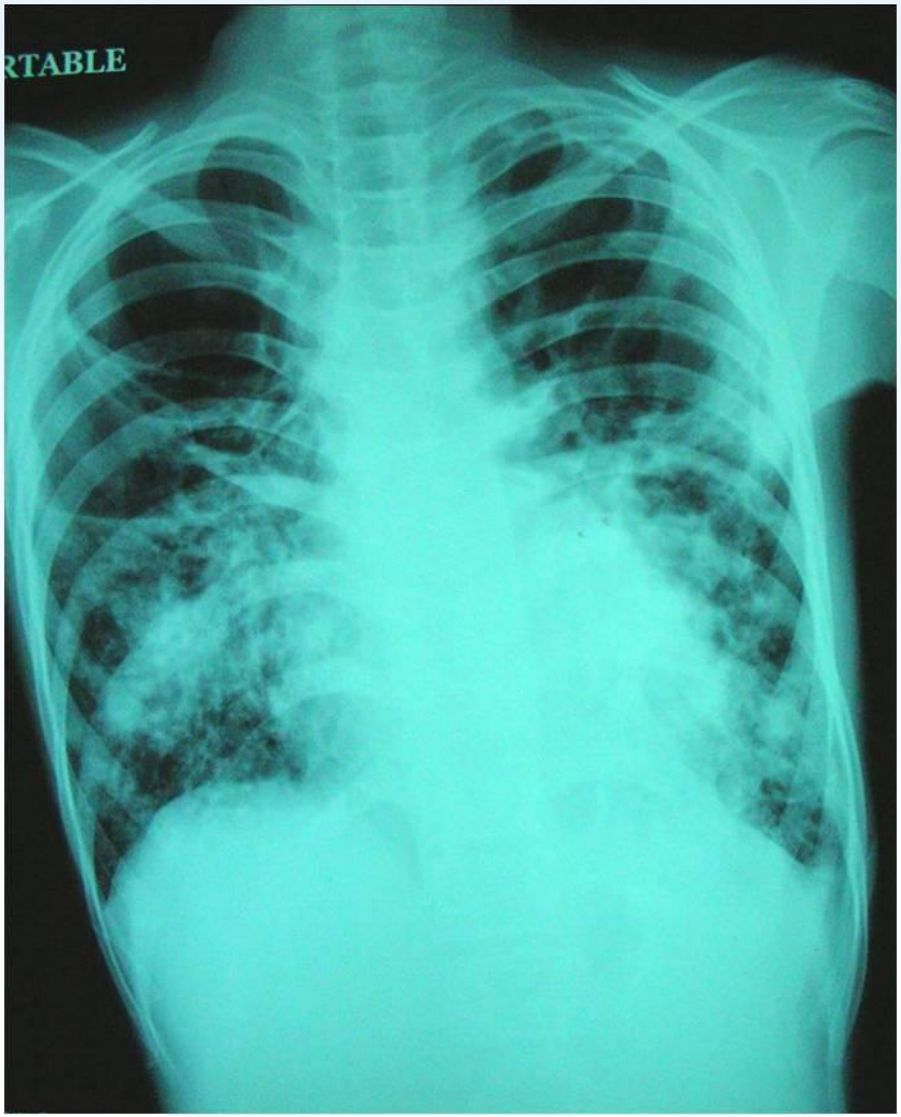
N = Number of studies

Modified DOT = DOT while hospitalization (or a portion)

Enhanced DOT = DOT with enablers (to assist pts. to complete Rx) + incentive

JAMA 1998;279:943-8.

Treating Adolescents is HARD



Case : A 15 year-old girl who does not want to take the meds

CXR at 9 M of treatment with poor compliance

Conclusion: Management of Childhood TB

- **Diagnosis: need better tests, invest in development of new tools & research**
- **Treatment: need more children friendly formulations, DOT, anti TB drugs for MDR/XDR**
- **Control: need active case finding and Rx in adults, prophylaxis to prevent TB in children**

ကျေးဇူးတင်ပါတယ်

THANK YOU

for your attention