Management of Childhood TB

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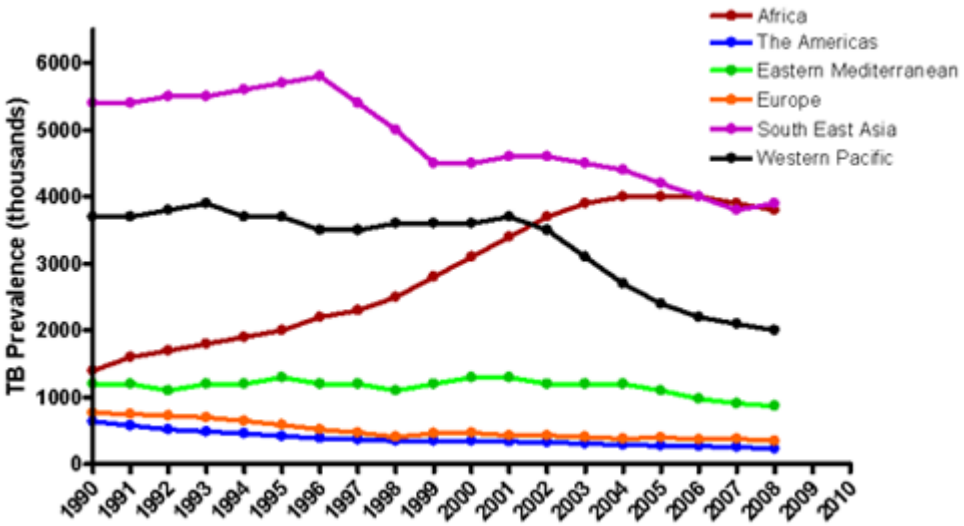
Epidemiology



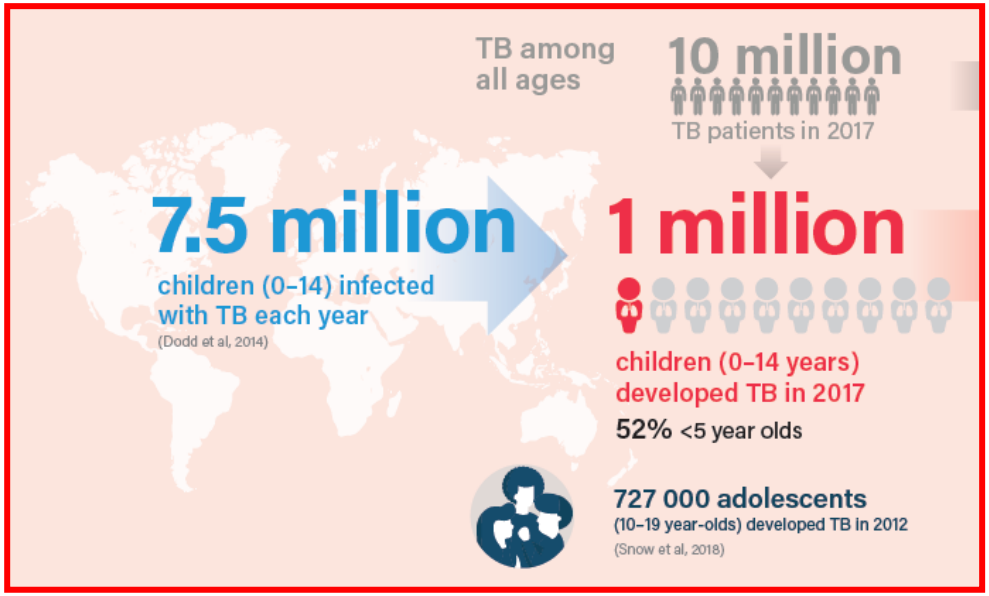
Global burden of Paediatric TB

- 1 m cases of child TB annually; **10-11%** of TB cases; > 15% high burden countries.
- A quarter of children with TB die from it;
  - Child TB mortality rate **23% vs 16%** in all TB cases
  - 17% TB deaths in HIV+ children
- Majority undiagnosed and untreated due to poor access to diagnostic and preventive services
- Estimated 25,000 children develop multi-drug resistant TB every year.

WHO 2018

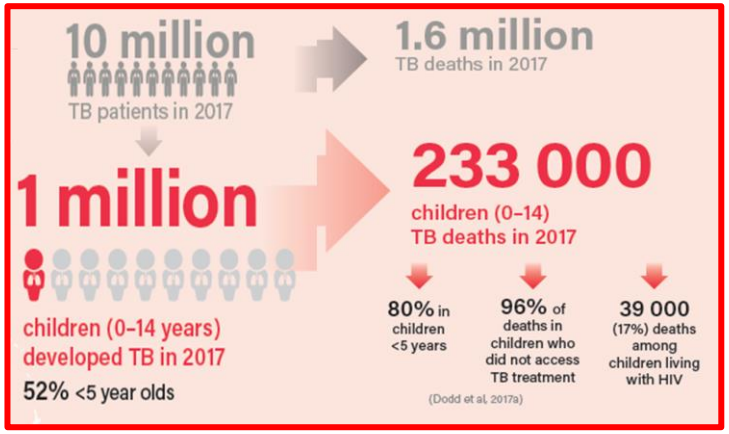
Dodd 2017

TB burden in children & adolescents

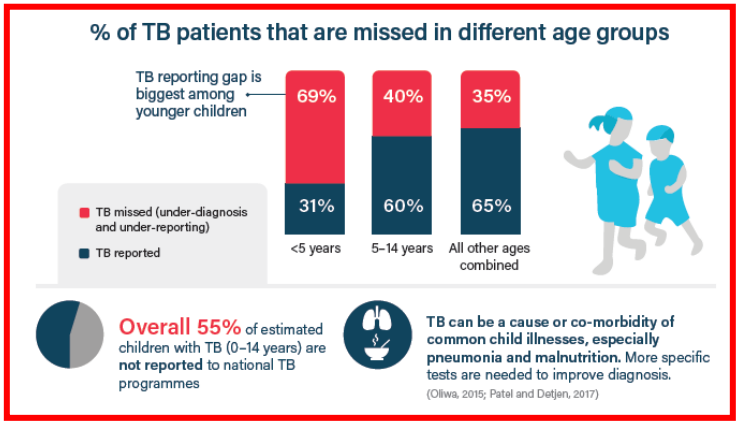


WHO 2018 Global TB report

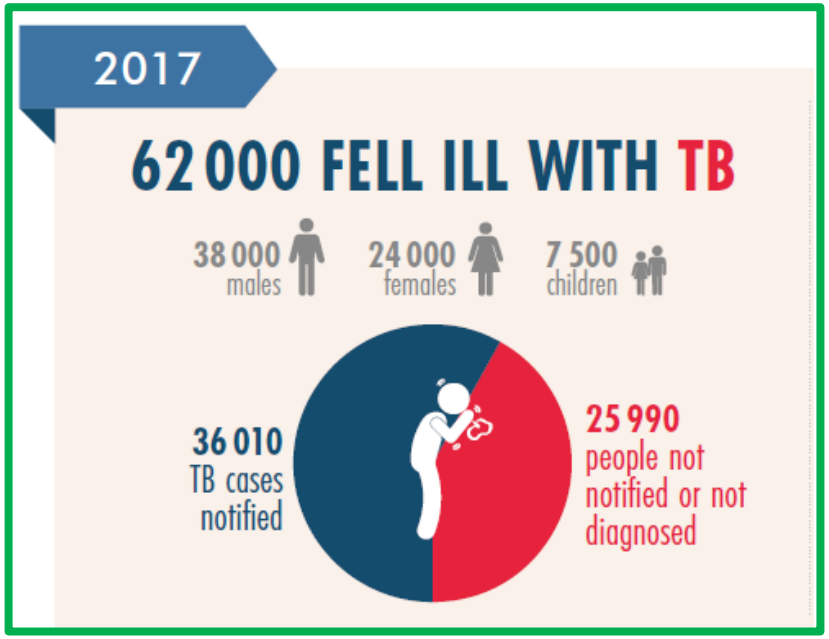
TB mortality in children

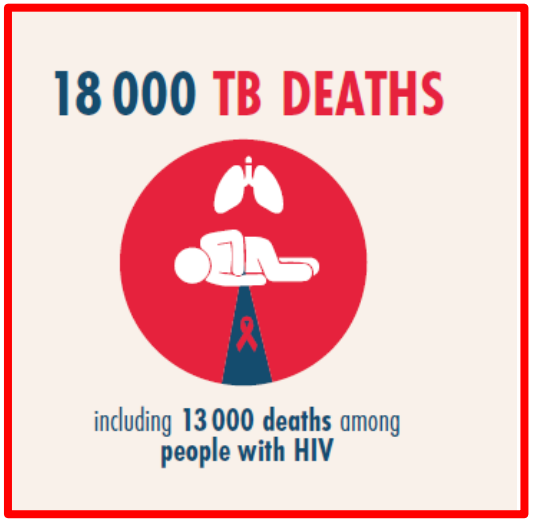


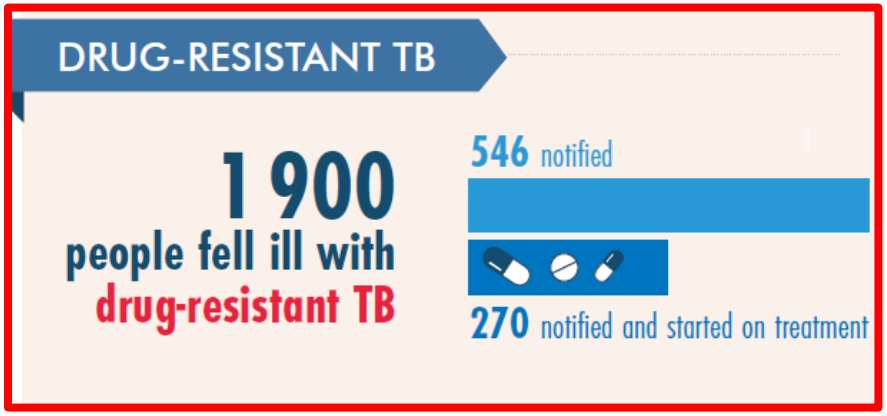
TB case detection gap in children



Zambia TB Profile



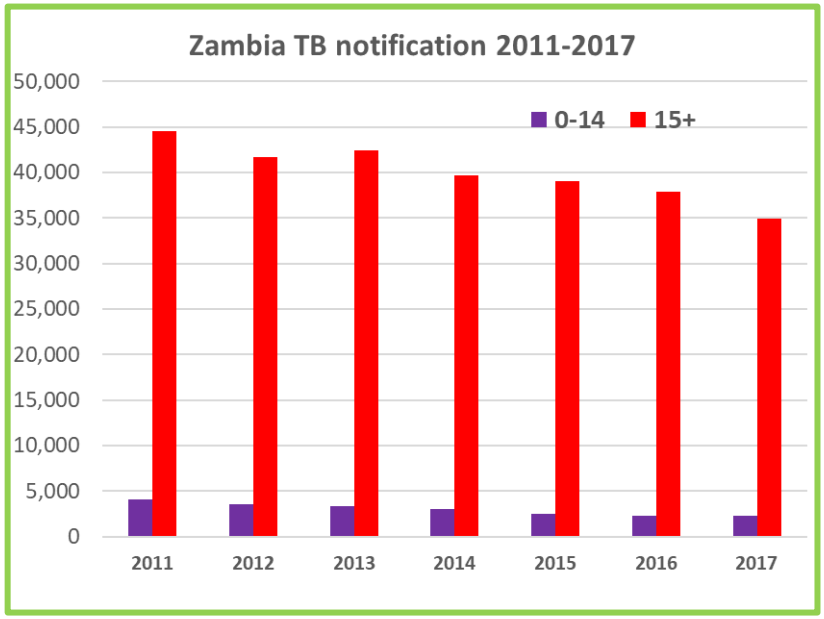




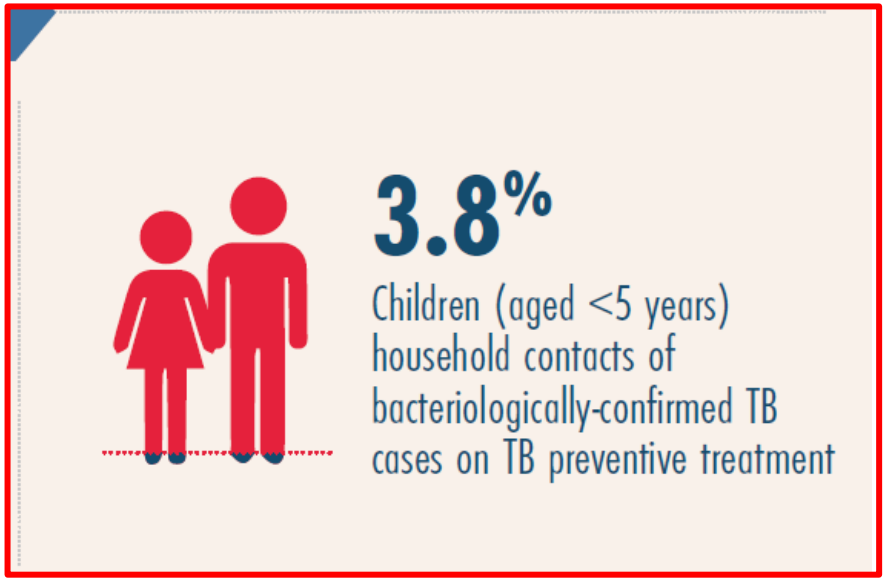
WHO 2018 Global TB report

Zambia TB Profile

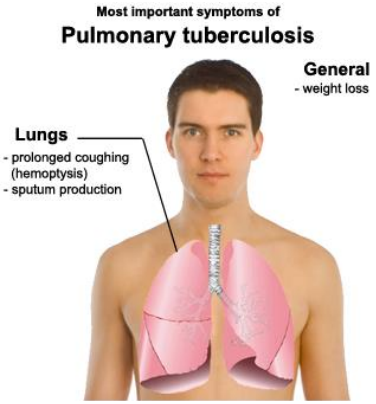
TB burden in children

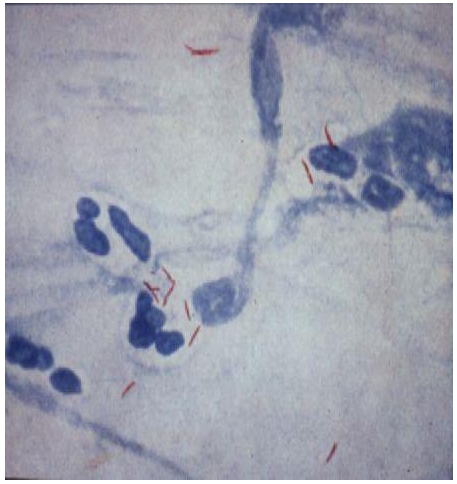


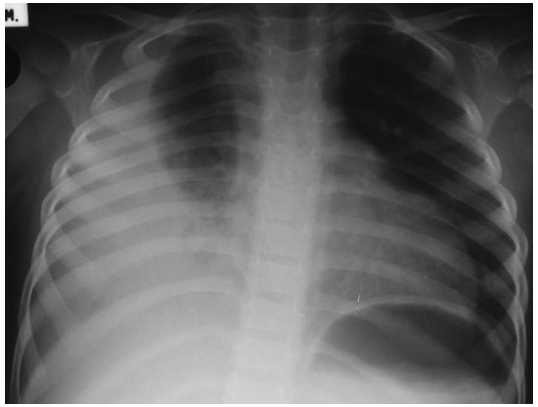
TB prevention in children

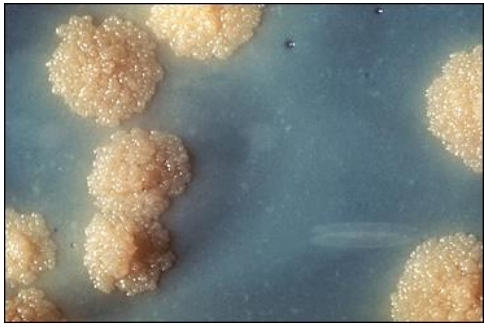


Diagnosis of child TB









Diagnostic Approach for childhood TB?

- DIAGNOSIS: Need at least 3/4 of the following elements

1. **Infection**
    1. Contact history (clinical history)
    2. Positive skin test (tuberculin skin test)

2. **Symptoms of chronic disease (Clinical history)**
    1. Cough, Fever, Weight loss, night sweats, reduced playfulness)

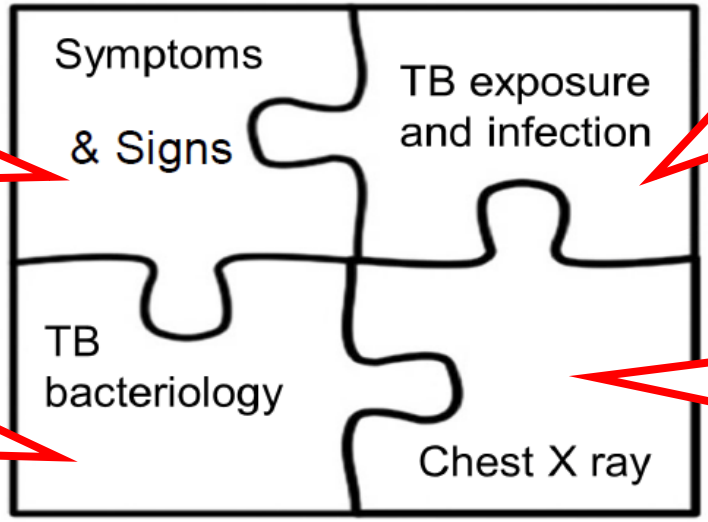
3. **Radiological changes suspicious of TB (Chest Xray)**

4. **Bacteriology (Smear microscopy, Gene-Xpert, MTB cultures, Urine LAM)**

TB diagnosis in children

Symptoms of chronic disease

Cough, Fever, Weight loss, night sweats, reduced playfulness



Risk of TB infection

TB contact history

Tuberculin skin test

TB Bacteriology

GeneXpert
Smear microscopy
Mycobacterial culture
Urine LAM

Abnormal CXR
Radiological changes suspicious of TB

Treatment of TB in children

Basic principles of TB treatment in children

- Same principles as adults
  - Cure the patient
  - Prevent relapse, death
  - Prevent development of drug resistance
  - Reduce transmission
  - Minimise toxicity
- Prolonged treatment with multiple drugs; ‘short course’
  - 6 months regimen
  - Intensive phase; 2 months
  - continuation phases ; 4 to 10 months
- Supervised treatment
  - Directly observed therapy

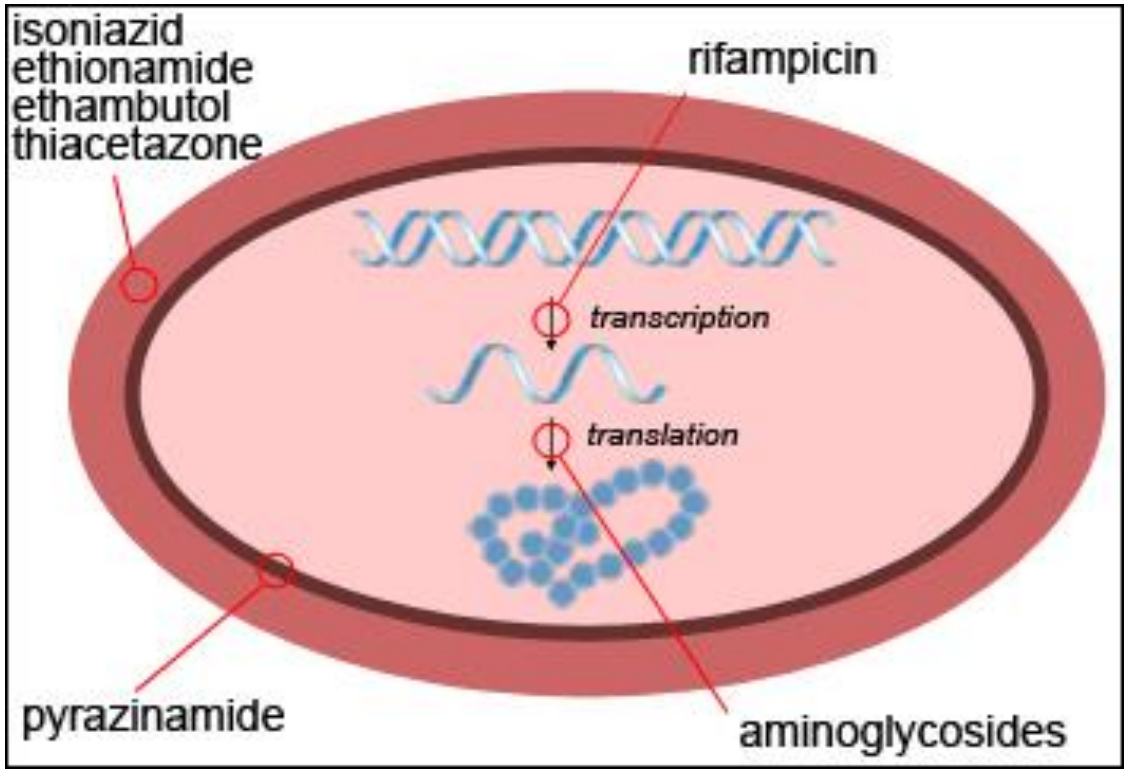
Considerations when initiating anti-TB treatment

- Type of disease
  - Severe (TBM, Miliary, Spinal) vs non-severe forms (lung, Pleura, LN)
- Regimens
  - In accordance with national TB programs
- Dosages
  - According to weight of child
  - Use of fixed dose combination tablets (FDCs)

Anti-tuberculosis drugs

- Isoniazid (INH or H)
- Rifampicin (RIF or R)
- Pyrazinamide (PZ or Z)
- Ethambutol (E)

Anti-TB Drugs



Role of Individual TB Drugs

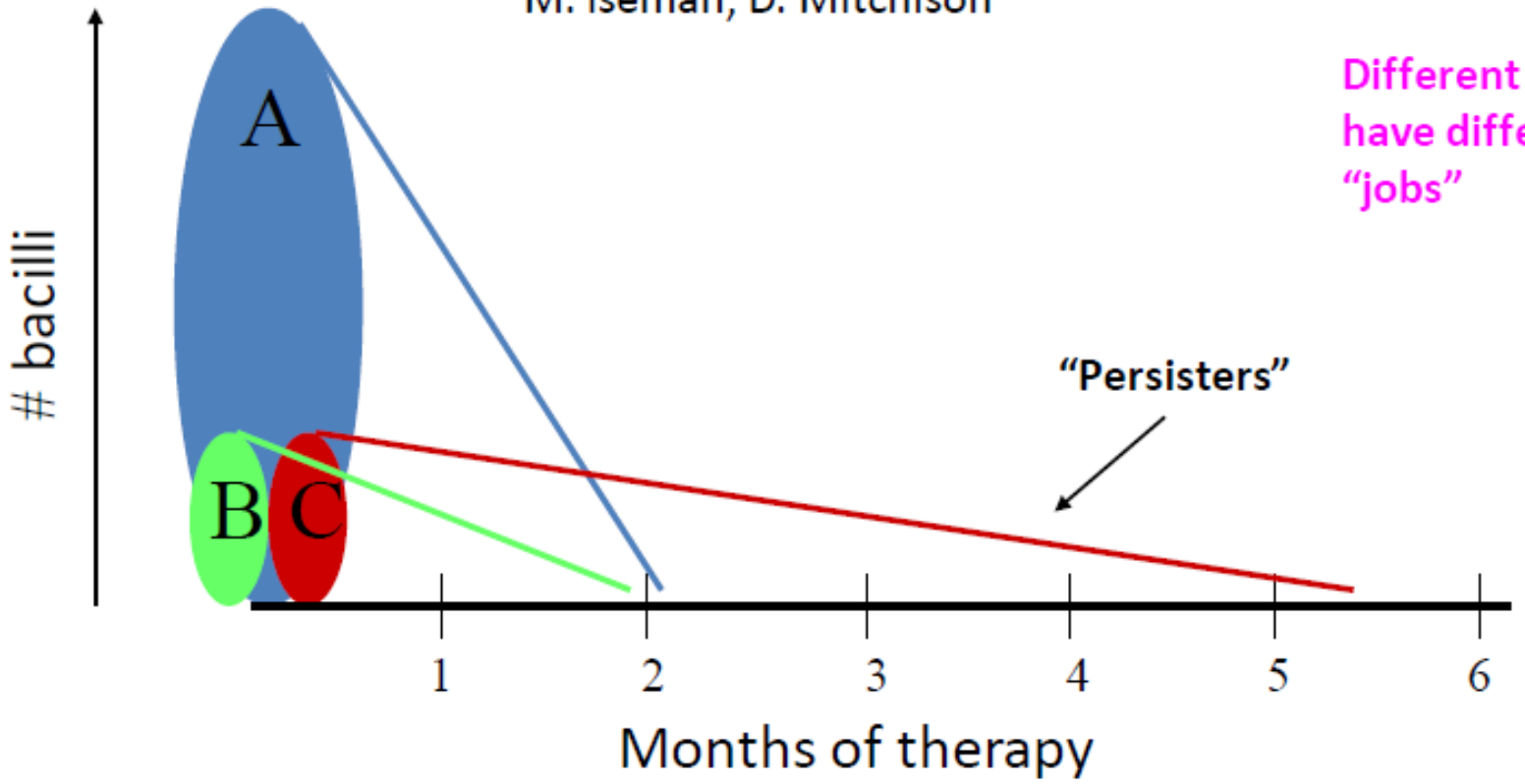
- **INH:** early bactericidal activity, rapid reduction in organism burden
- **Rifampin:** unique sterilizing activity against "persisters", key contributor to cure without relapse
- **Pyrazinamide:** sterilizing activity in acidic environments over the first 2 months, allowing for shortening of treatment
- **Ethambutol:** prevents resistance to other antibiotics

Presented by: Kelly Dooley MD, PhD
Johns Hopkins University School of Medicine
Division of Clinical Pharmacology

Hypothetical Model of TB Chemotherapy

3 anatomic/metabolic populations of bacilli in cavitary TB

M. Iseman, D. Mitchison



A: rapid multiplication, isoniazid (INH)>rifampin>ethambutol

B: slow multiplication, acidic environment, pyrazinamide>rifampin>INH

C: sporadic multiplication, rifampin>isoniazid

Presented by: Kelly Dooley MD, PhD
Johns Hopkins University School of Medicine
Division of Clinical Pharmacology

TB regimens for children

TB disease category	Recommended regimen	
	Intensive phase	Continuation phase
All forms of PTB and EPTB except TBM and osteoarticular TB	2 HRZE	4 HR
TB meningitis Osteoarticular TB	2 HRZE	10 HR

Recommended dosages

isoniazid (H)	**10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day**
rifampicin (R)	**15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day**
pyrazinamide (Z)	**35 mg/kg (range 30–40 mg/kg)**
ethambutol (E)	**20 mg/kg (range 15–25 mg/kg)**

1. **Four drugs (RHZE) in intensive phase for all new cases in HIV endemic setting**
2. **Streptomycin no longer recommended for first-line therapy**
3. **12-month regimens for TBM and osteo-articular TB**

New fixed dose combinations

For the intensive phase:

- RMP 75mg + INH 50mg + PZA 150mg

For the continuation phase:

- RMP 75mg + INH 50 mg

Weight bands using the New Ped FDCS

	Intensive Phase		Continuation Phase
Weight bands	50H, 75R, 150Z	100E	50H, 75R
3.0-3.9	0.75	0.75	0.75
4.0-7.9	1	1	1
8.0-11.9	2	2	2
12.0-15.9	3	3	3
16.0-24.9	4	4	4
≥ 25.0kg	Adult formulation	Adult formulation	Adult formulation

Ethambutol provided as separate 100mg tab

Use of ethambutol in children

- Ethambutol is recommended as fourth drug in intensive phase of first-line regimens
- Risk of toxicity is dose-related and related to duration of therapy
- The risk of toxicity is **negligible** for children of any age when ethambutol is used at recommended dosages – especially as duration is usually limited to 2 months
- **Ethambutol can be safely used at recommended dosages in all ages**

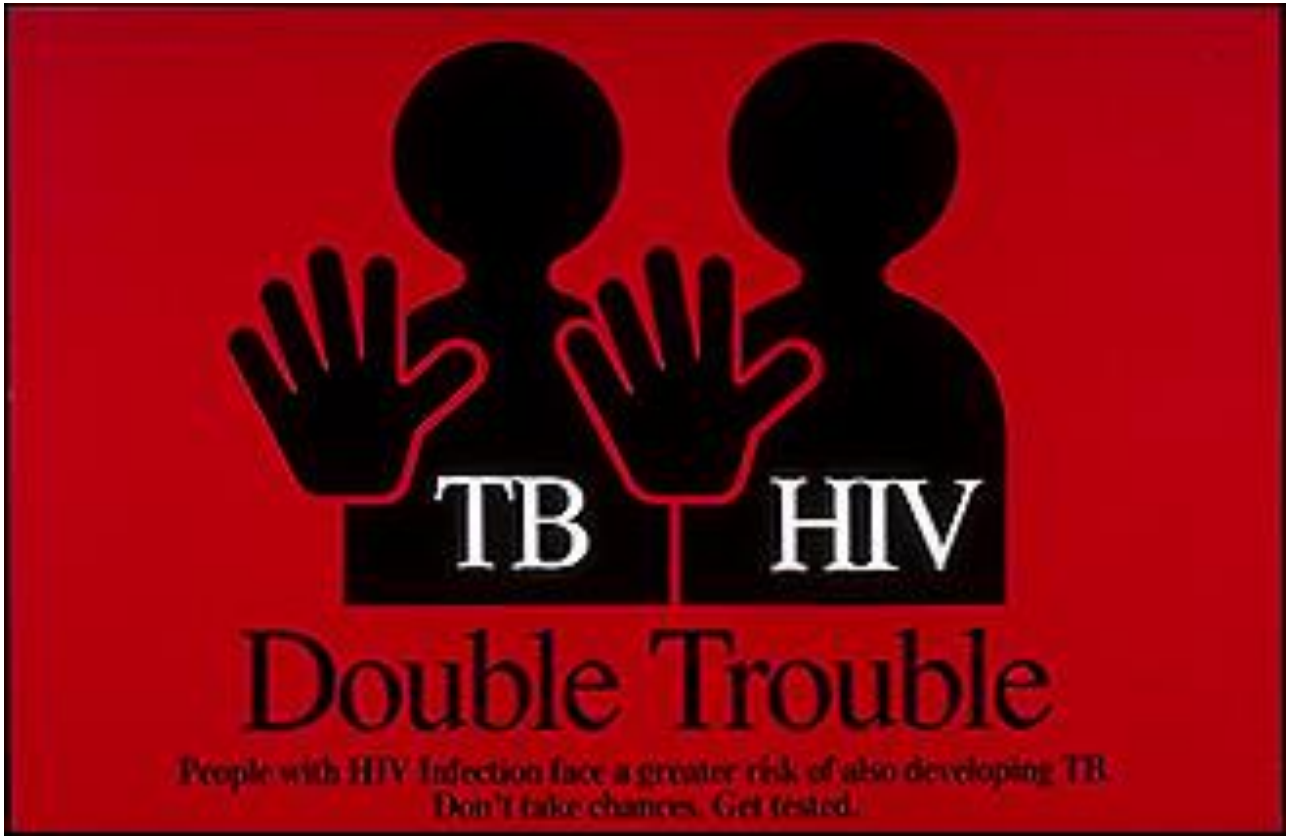
Common side effect of TB drugs

- **Rifampicin**
  - Hepatitis, discoloration of body fluids,
  - GI; nausea, vomiting
- **Isoniazid**
  - Peripheral neuropathy
  - Hepatitis
- **Ethambutol**
  - Optic neuritis
- **Pyrazinamide**
  - Hepatitis
  - Joint pains
- **Streptomycin**
  - Auditory & vestibular toxicity
  - Renal toxicity

TB treatment & toxicity in children

- TB drugs are well tolerated in children
- Adverse effects unusual; hepatitis most important

TB/HIV


TB
HIV
Double Trouble
People with HIV Infection face a greater risk of also developing TB.
Don't take chances. Get tested.

Child TB management and HIV

Principles of treatment of TB in HIV-infected children is similar to HIV-uninfected children

ART improves outcome for HIV-infected children treated for TB

It is recommended that HIV-infected children receive

1. Four first-line drugs (RHZE) in intensive phase for suspected or confirmed drug-sensitive TB irrespective of severity of disease
2. Similar duration of regimens as for HIV-uninfected
3. ART as recommended within 2-8 weeks of starting TB treatment or continue ART
4. Cotrimoxazole preventive therapy
5. Pyridoxine supplement
6. Nutritional support

HIV-infected children are at increased risk of relapse and drug resistant TB

Consideration when treating TB-HIV co-infection

- Same principles, drug & duration for HIV(+) vs HIV(-)
- Drug interactions
  - Rifampicin reduces serum levels of NVP, PIs (LPV/r, ATZ), DTG and TAF increasing risk of HIV treatment failure
- Common side effects
  - Hepatotoxicity: Nevirapine, INH, d4T
  - Peripheral neuropathy; INH, Thymidine analogues
- Timing of ART initiation
  - Start ART within 2-3 wks of ATT initiation
- Alternatives

TB AND ART DRUG INTERACTIONS

Overcoming the inducing effect of rifampicin

- Use EFV
- Super-boosting of LPV/r with additional Ritonavir from 4:1 to 1:1
- Double-dose DTG (from DTG OD to DTG BD)
- Double-dose TAF (OD to BD)
- Triple nucleoside option (AZT+3TC+ABC)
- Replace Rifampicin with Rifabutin(not available on current Zambian TB guidelines)

TB AND ART TREATMENT OPTIONS

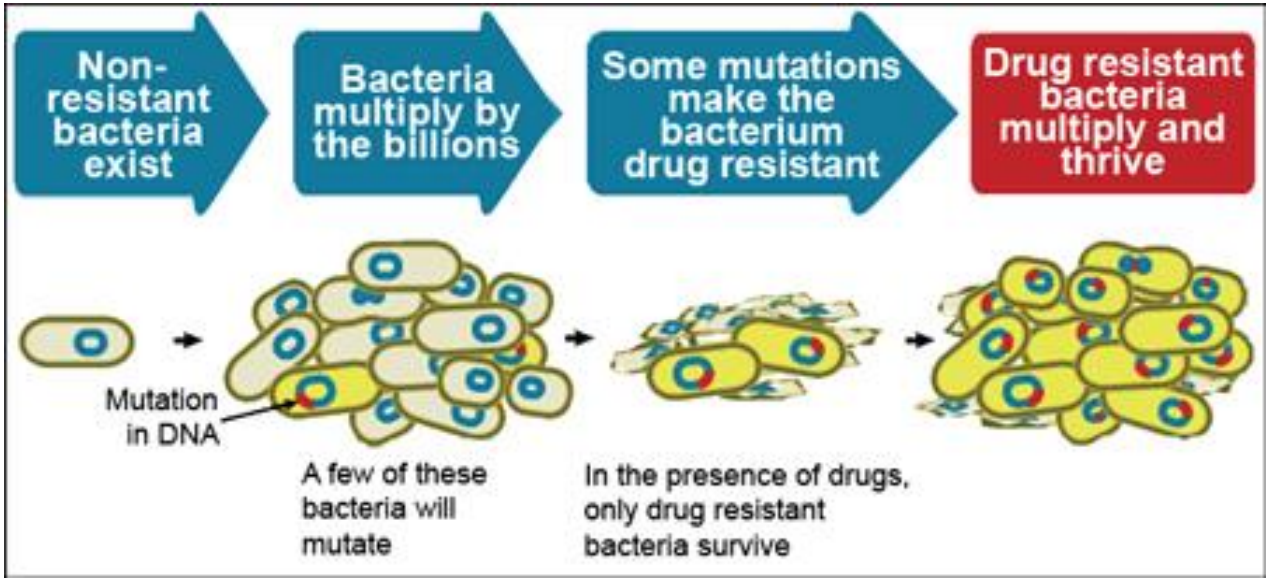
Specific Populations	Description	Preferred 1st line ART	Alternative regimen
Children co-infected with TB	<20 kg	ABC + 3TC + RAL (Double dose of RAL) or ABC + 3TC + AZT	AZT + 3TC + EFV (> 3 months)
	20 – 29.9 kg	ABC + 3TC + DTG Increase the frequency of DTG to 50mg twice daily	ABC + 3TC + LPV-r (LPV-r should be superboosted, otherwise consult expert opinion) ABC + 3TC + EFV ABC + 3TC + RAL
	≥ 30Kg	TDF + 3TC + DTG Increase the frequency of DTG to 50mg twice daily	

Overlapping toxicities of ART & ATT

Table 1. Overlapping toxicities associated with antiretroviral and antituberculosis drugs.

Toxicity	Antiretroviral drugs	Antituberculosis drugs
Hepatitis	Nevirapine, protease inhibitors	Rifampicin, isoniazid, pyrazinamide, ethionamide
Rash	Nevirapine, efavirenz, abacavir	Rifampicin, isoniazid, quinolones
Anemia, neutropenia	Zidovudine	Rifampicin, isoniazid
Nausea, vomiting	Zidovudine, ritonavir, indinavir	Rifampicin, pyrazinamide, quinolones, ethionamide
Peripheral neuropathy	Stavudine, didanosine, zalcitabine	Isoniazid, ethambutol, cycloserine
CNS symptoms	Efavirenz	Streptomycin, quinolones, cycloserine

Multi-Drug resistant TB



Definitions

1. **Mono-resistant**: Resistance to a single anti-TB drug
2. **Poly-resistant**: Resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin)
3. **Multidrug-resistant (MDR):** Resistance to both isoniazid and rifampicin, with or without resistance to other first-line anti-TB drugs
3. **Extensive drug resistance (XDR-TB):** This is an MDR-TB that is resistant to any one of the fluoroquinolones and to at least one of three injectable second line anti TB drugs
4. **Rifampicin resistance**: It is resistance to Rifampicin in the form of monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

MDR TB

- **Multi-drug resistant TB (MDR TB)**
  - Resistance to at least isoniazid and rifampicin

Initiating treatment for MDR TB in children

Indication to initiate MDR TB in children;

- **Confirmed MDR TB by DST**
- **RR on Xpert MTB/RIF**
- **A smear Positive with confirmed MDR contact**
- **A probable diagnosis of MDR TB in a child with unconfirmed DST who is not responding to standard TB therapy and is a known contact of an MDR TB case**

DR-TB Treatment Regimen

- Two regimen now recommended:
  I. Shorter regimen (standardised)
  II. Individualised regimen containing new and repurposed drugs

Regimens for treatment of MDR-TB
- more toxic, less potent
- take longer
- more expensive
- less evidence-based than standard therapy

Longer 20 months regimen

8 Km-Lfx-Eto-Cs-Z/
12 Lfx-Eto-Cs-Z (+B6)
Duration: 20 months

Challenges:

- *More cost*
- *Multiple adverse effects*
- *Challenges in adherence (20 months)*
- *Poor treatment outcomes (≈ 50%)*

Shorter Regimen

4-6 Km-Mfx-Cfz-Eto-Z-E-H^{HD}/
5 Mfx-Cfz-E-Z (+B6)
Duration: 9 to 11 monthS

Advantages:

- *lower cost*
- *Less side-effects*
- *Increased potential for adherence*
- *Better treatment outcomes (≈ 80%)*

Shorter MDR TB regimen

- The shorter regimen for RR-TB and MDR-TB patients is for 9-11 months

Who qualifies for the shorter regimen?

- RR-TB /MDR-TB who were not previously treated with second line drugs
- Patients in whom resistance to fluoroquinolone and injectable has been excluded or is considered highly unlikely

CHOOSING THE MDR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

CRITERIA: Do any of the following apply ?

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

NO

Shorter MDR-TB regimen

Intensive phase
Duration: 4-6 months
Composition: 4 second-line drugs

Continuation phase
Duration: 5 months
Composition: 2 second-line drugs

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

YES

Individualised ("conventional") MDR/RR-TB regimens

Intensive phase
Duration: Up to 8 months
Composition: 4 or more second-line drugs

Continuation phase
Duration: 12 months or more
Composition: 3 or more second-line drugs

Groups of drugs used in DR-TB Treatment

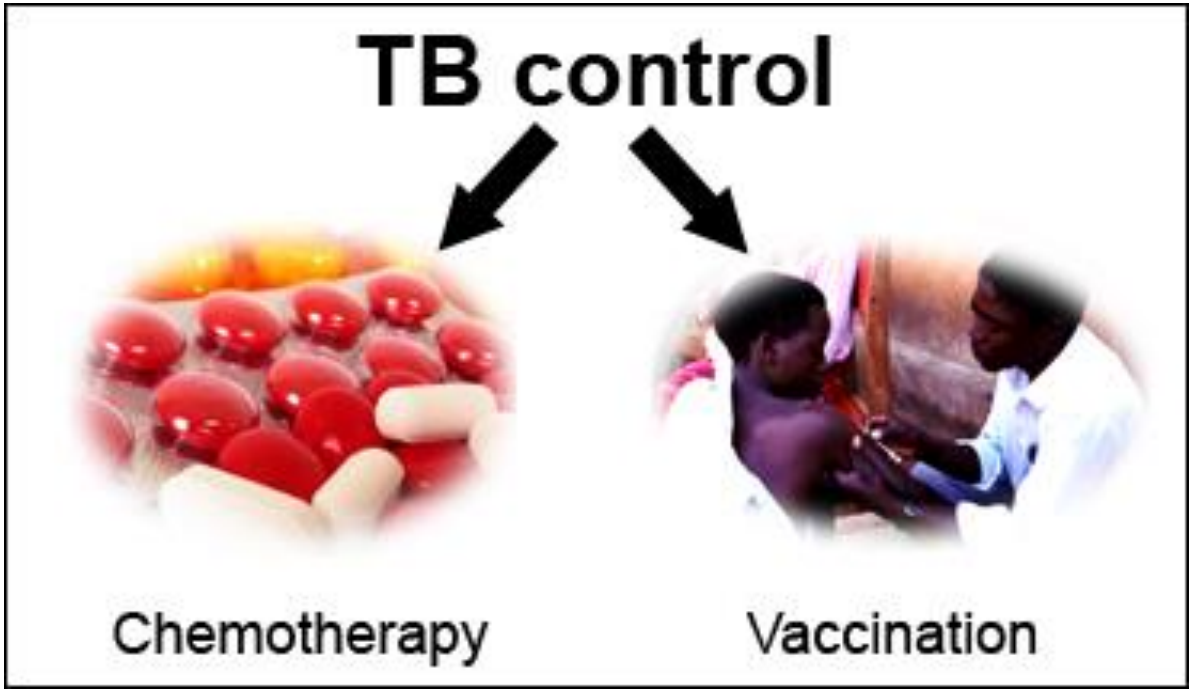
Table 6. Medicines recommended for the treatment of RR-TB and MDR-TB[a]

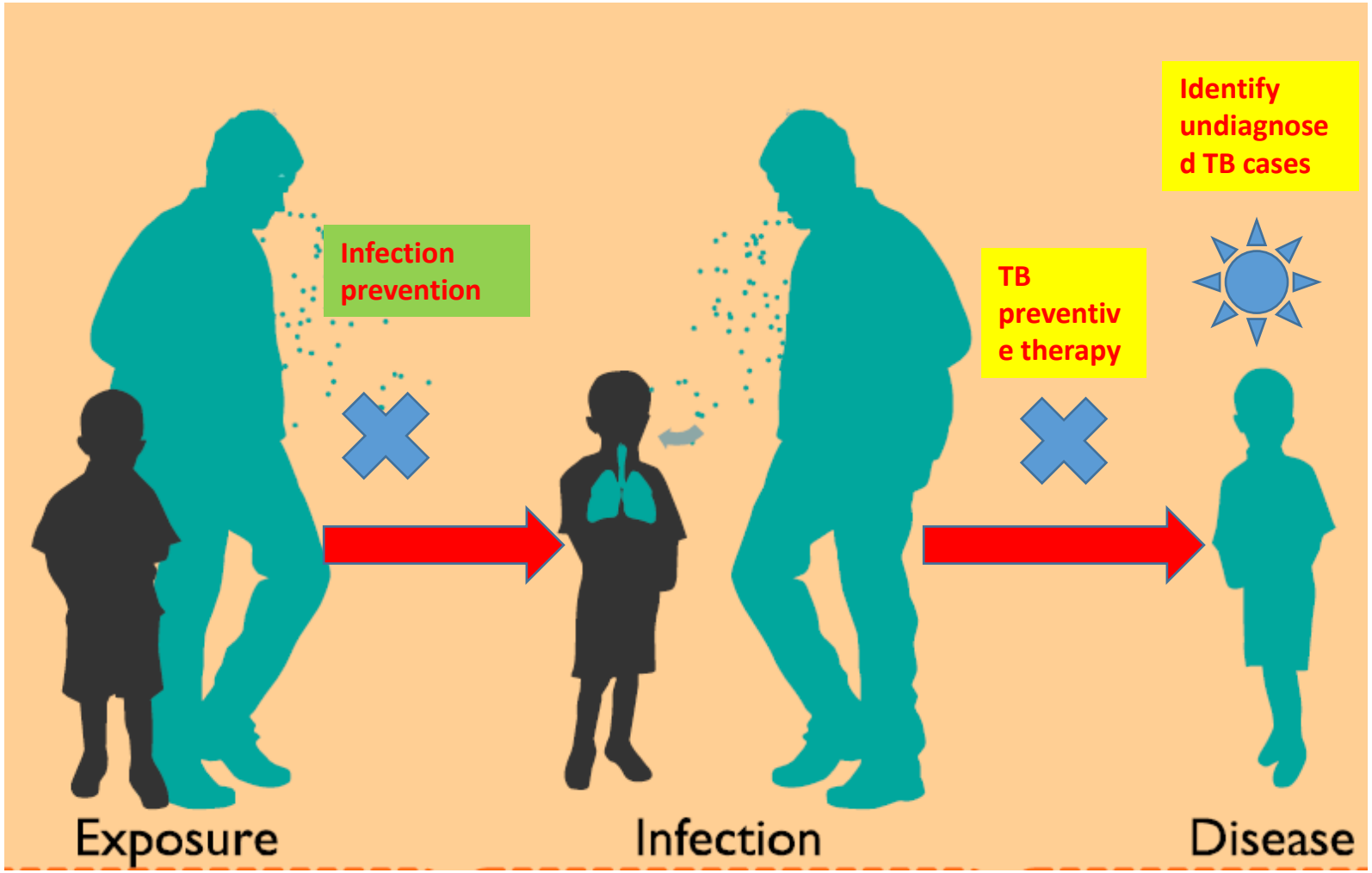
Group A. Fluoroquinolones[b]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
Group B. Second-line injectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[c]	(S)
Group C. Other core second-line agents[b]		Ethionamide / prothionamide	Eto / Pto
		Cycloserine / terizidone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	H[h]
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	*p*-aminosalicylic acid	PAS
		Imipenem–cilastatin[d]	Ipm
		Meropenem[d]	Mpm
		Amoxicillin-clavulanate[d]	Amx-Clv
		(Thioacetazone)[e]	(T)

SECOND LINE TB DRUGS AND THEIR COMMON ADVERSE EVENTS

DRUG	*ADVERSE EFFECTS*
Ethionamide, Prothionamide	Gastrointestinal disturbance, hepatitis, hypothyroidism
P-aminosalicylic acid	Gastrointestinal disturbance, hepatitis, hypothyroidism
Cycloserine / Terizidone	Neurological and psychiatric disturbances: headache, irritability, depression , seizures, suicidal ideas.
Kanamycin, Amikacin, Capreomycin	Pain at injection site, hypokalemia and hypomagnesaemia, nephrotoxicity, ototoxicity, peripheral neuropathy.
Ofloxacin, levofloxacin, gatifloxacin,moxifloxacin	Generally well tolerated, occasional gastrointestinal disturbance, joint pain.

TB prevention in children

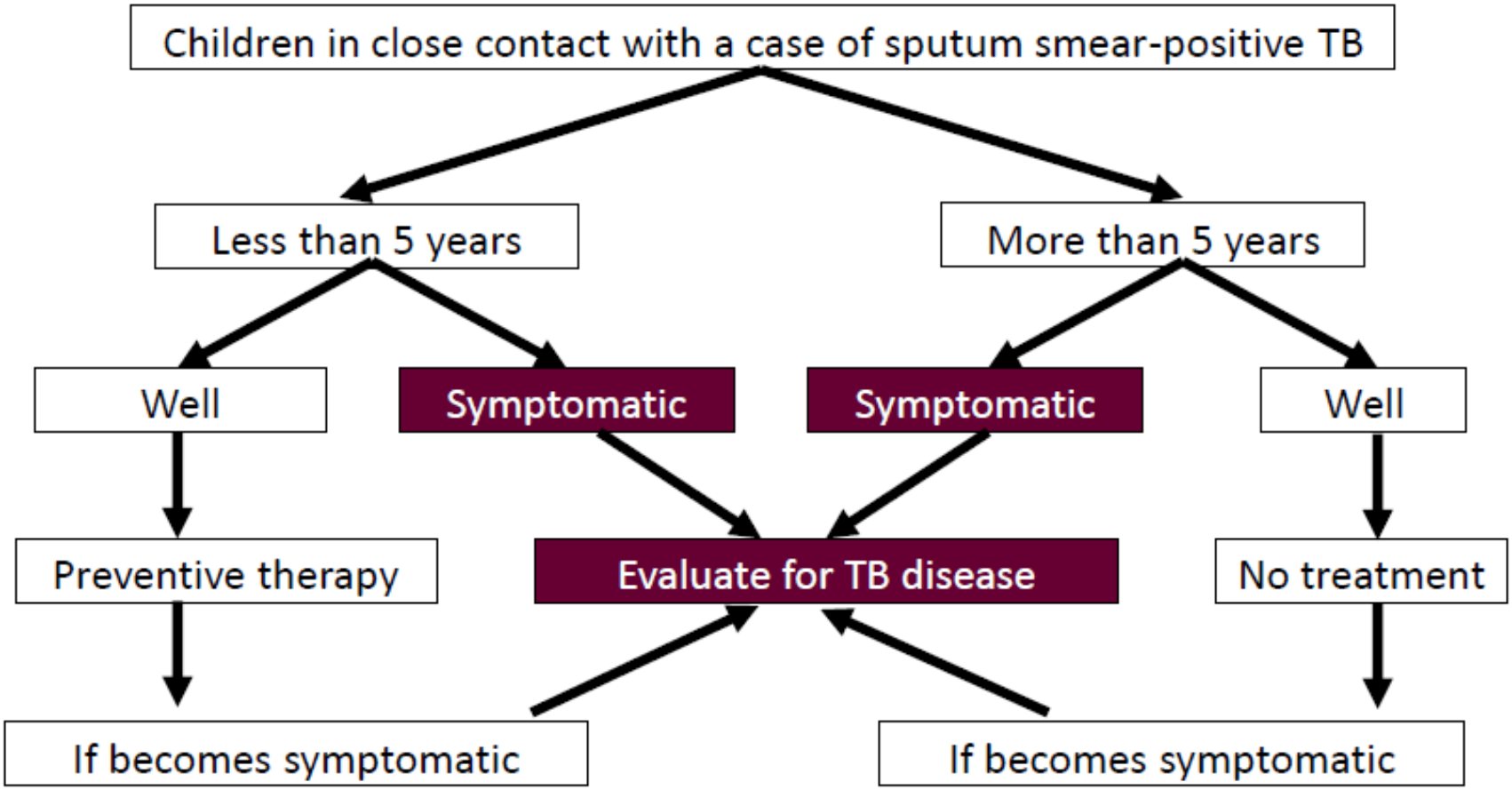



Identify undiagnose d TB cases
Infection prevention
TB preventiv e therapy
Exposure
Infection
Disease

TB prevention in children

- BCG
  - Given at birth
  - Not fully protective except for severe forms; TBM, Milliary, Spinal TB, disseminated
- Assessment of children in contact with smear positive adults
- Screen for TB in HIV infected children; 3 ‘I’s approach
  - Intensified case finding
  - Isoniazid preventive therapy
  - Infections prevention
- Identify & adequately treat infected adults

WHO symptom based screening



Note that contact screening has two important roles

1. **Active case-finding**
2. **Preventive therapy for at-risk contacts without TB**

Isoniazid preventive therapy (IPT)

- Isoniazid preventive therapy
  - Asymptomatic under-5 contacts of smear positive TB
  - HIV infected patients; 0-10 years
    - Screen for TB at every contact
    - IPT after ruling out active TB disease
- 6 months course of INH at 10mg/kg

New recommendations for TB preventive therapy in Zambia

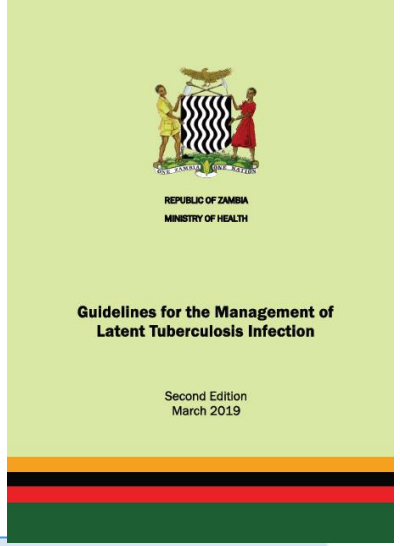


Table 2 Recommended dosages of drugs for the treatment of LTBI

Drug regimen	Dose per kg body weight	Maximum dose
Isoniazid alone, daily for 6 or 9 months	Adults, 5 mg Children, 10 mg (range, 7–15 mg)	300 mg
Daily rifampicin alone for 3–4 months	Adults, 10 mg Children, 15 mg (range, 10–20 mg)	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid: Adults, 5 mg Children, 10 mg (range, 7–15 mg) Rifampicin Adults, 10 mg Children, 15 mg (range, 10–20 mg)	Isoniazid, 300 mg Rifampicin, 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Individuals aged ≥ 12 years: Isoniazid: 15 mg Individuals aged 2–11 years: isoniazid: 25 mg Rifapentine: 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–50.0 kg = 750 mg > 50 kg = 900 mg	Isoniazid, 900 mg Rifapentine, 900 mg

Thank you