





## It began here....

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# Management strategies evolved..

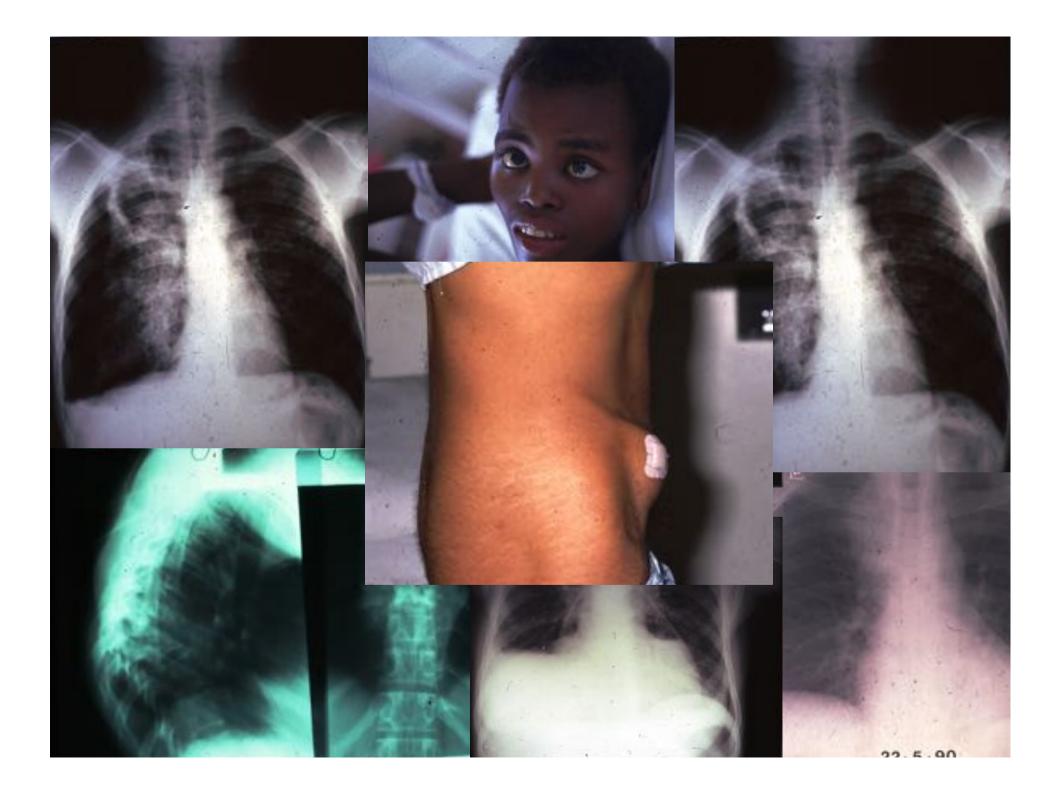


## And evolved



## Till now...





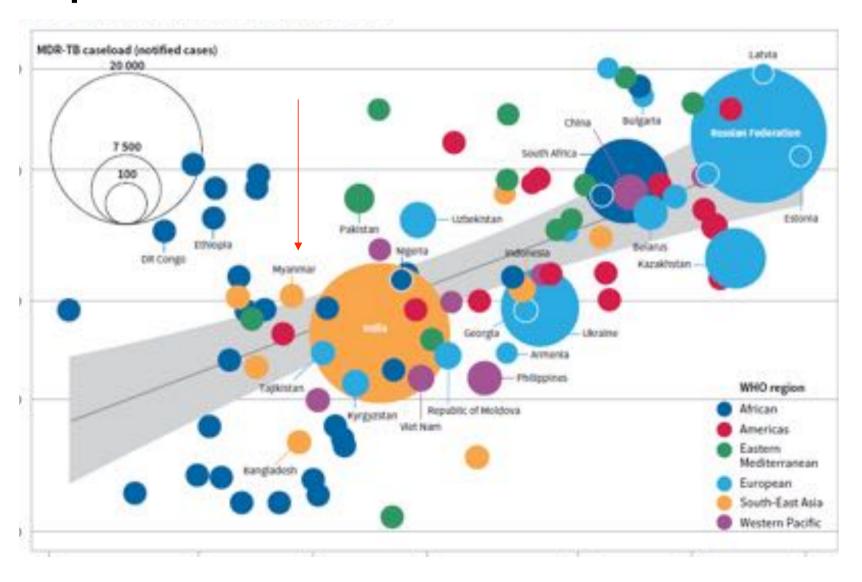
## Today

- Global and Myanmar
- Principles of treatment
- MDRTB, XDRTB and TDRTB

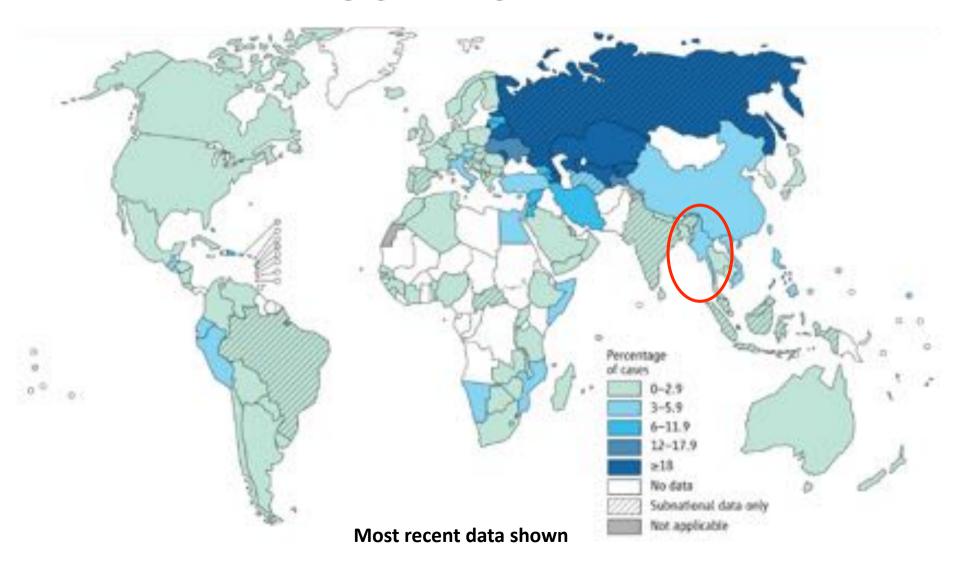
## MDRTB globally

- Globally, 5% of TB cases are estimated to have MDR-TB.
  - Primary TB an estimated 3.5%
  - Secondary TB an estimated 20.5%
- Levels of drug resistance among new cases are <3% in 108 (75%) of the 144 countries with drug resistance surveillance data</li>
- Eastern European and central Asian countries have the highest levels of MDR-TB
  - Primary TB an estimated 35%
  - Secondary TB an estimated 75%

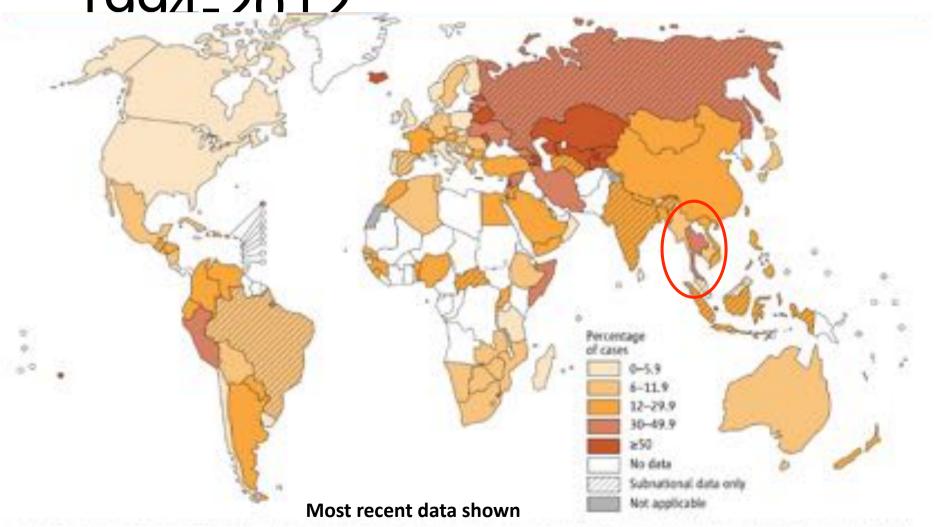
## **Epidemic of MDRTB**



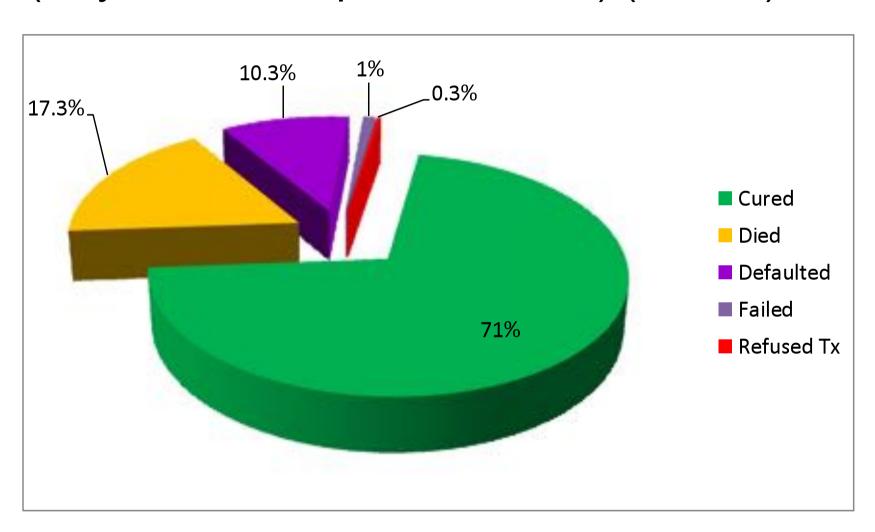
# Percentage of new cases with MDRTB 1994-2012



Percentage of previously treated TB cases with MDRTB



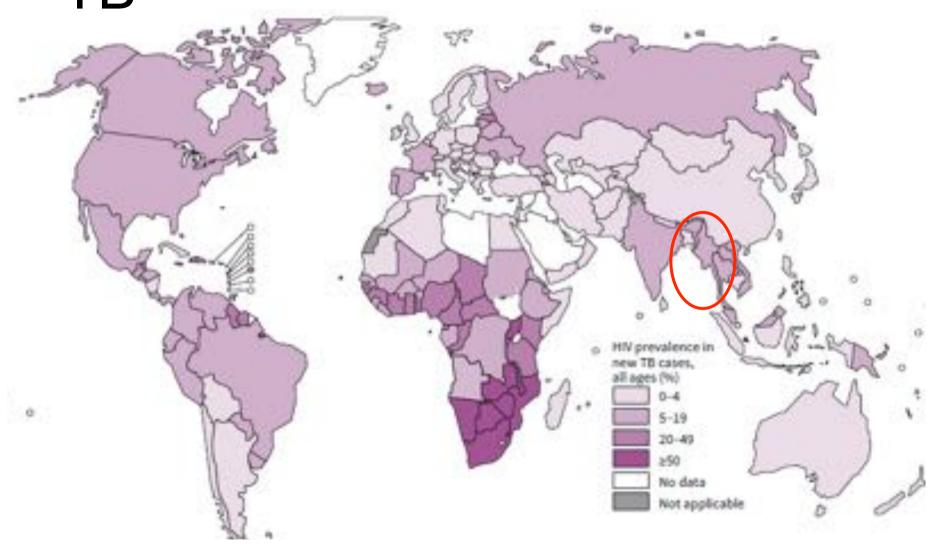
# MDR-TB treatment outcomes of Myanmar (July 2009 to September 2011) (N=303)



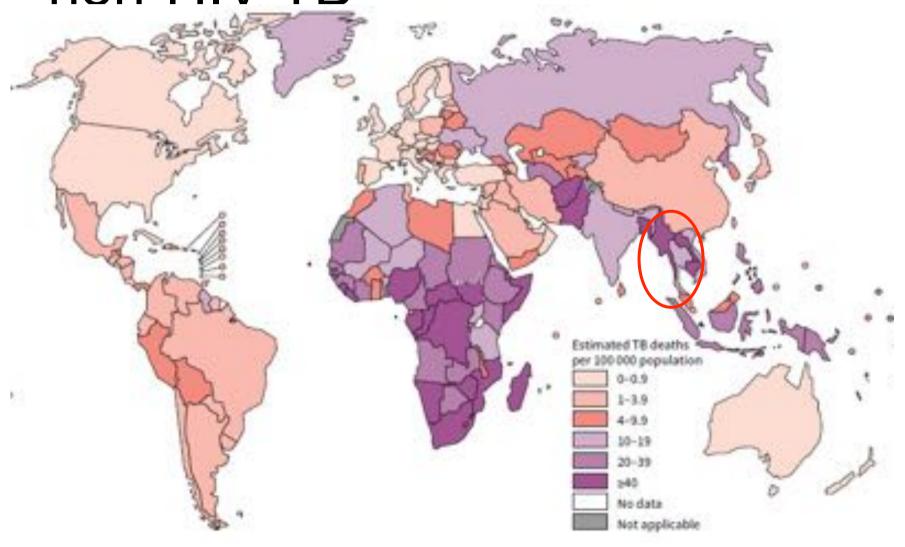
# Countries that have notified at least 1 patient of XDRTB by 2012



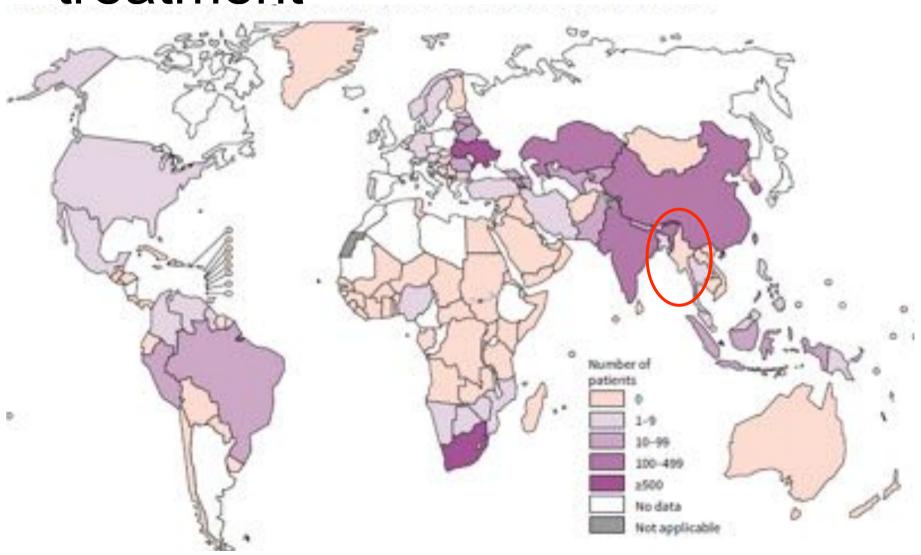
# Estimated HIV prevalence in TB



Estimated TB mortality rates in non-HIV TB



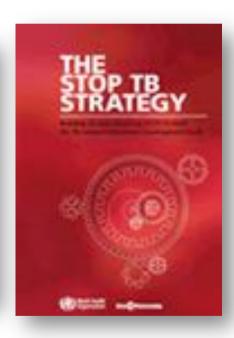
# Number of XDRTB started on treatment



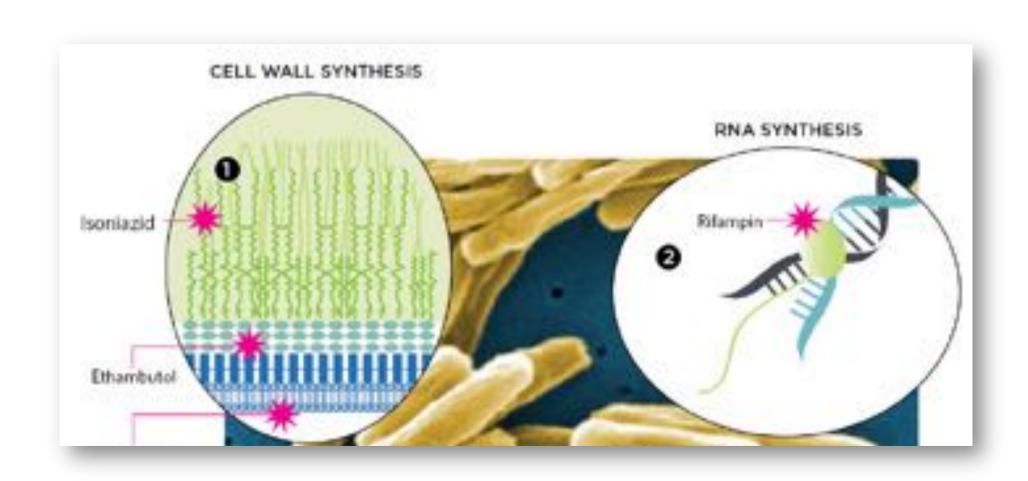
## Why has MDRTB occurred?



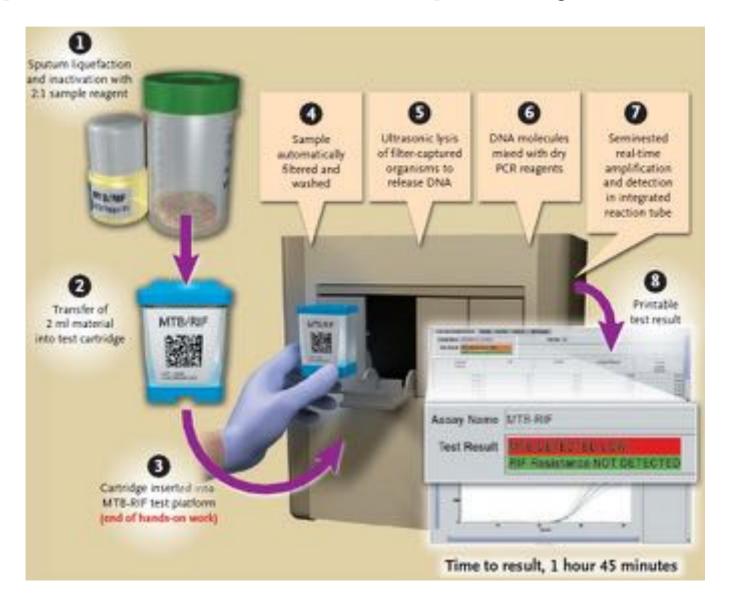




## Current drug activity



## **Xpert MTB/RIF capacity**



# Other resistance will develop - genes associated with resistant MTB

**Drug** Gene

Isoniazid Kat G, Inh A, Kas A

Rifampicin rpo B

Ethambutol emb B

Streptomycin rps L

Pyrazinamide pnc A

Fluoroquinolones gyr A

## Principles of MDR+ treatment

- Promptly suspect drug-resistant (DR) TB and do full TB screen AND initiate appropriate therapy early if likely
- Regimens should be based on the history of drugs taken by the patient
- Assume R if therapy given previously
- R prevalence in country of birth/residence MUST be taken into consideration
- If the evidence for drug sensitivity is unclear DO NOT rely on it being fully active

## Basic rules...

- Give AT LEAST 4 active drugs (= 6-7 drugs usually because uncertain) while awaiting sensitivities
- Drugs are chosen with a stepwise selection process
- The duration of the intensive phase of treatment (when an injectable drug is given) should be at least 6 months (or 4 months after culture conversion).
- The continuation phase (without the injectable drug) should last until 18 months after culture conversion

## Principles of MDR+ treatment

- When possible, give PZA, EMB, and MOX once per day as thought high peaks may be more efficacious.
- PRO, CYC, PAS usually split because decreases AE
- Monitor levels of AMIK/KAN as may be needed for up to six months
- The minimum length of treatment for XDR-TB will be 18 months after culture conversion
- PZA can be used for full course of treatment
- Consider surgery if localised disease

## When to include...

- Group 1 drugs:
  - INH
  - Rifampicin
  - Pyrazinamide
  - Ethambutol

## FIRST - 1<sup>st</sup> line drugs

- Most potent and best tolerated
- MUST be used if MDRTB suspected but unconfirmed
- MUST not rely on and assume resistance is present and therefore add in additional drugs
- If RIF resistance then rifabutin will also be resistant in 85%
- If INH resistant then may be PRO/ETH resistant

## When to include/which one...

- Group 2 drugs injectables:
  - Streptomycin
  - Kanamycin
  - Amikacin
  - Capreomycin

## SECOND - INJECTABLE

- All patients with possible MDR+ TB MUST receive an injectable agent
- All patients SHOULD receive AMIK or KAN if susceptibility is documented or presumed
- There are high rates of streptomycin resistance in DR-TB patients
- AMIK/KAN have low otoxicity rates but get BL audiometry
- AMIK/KAN usually X-resistant
- If an isolate is resistant to SM/AMIK/KAN, capreomycin should be used

## When to include/which one...

- Group 3 drugs fluoroquinolones
  - Ciprofloxacin
  - Ofloxacin
  - Levofloxacin (dose)
  - Moxifloxacin

## THIRD – Quinolone

- All patients should receive quinolone unless R very likely.
- Ciprofloxacin should NO longer be used to treat TB
- Most potent: MOX = GAT > LEV > OFL
- MOX/LEVO may have activity against CIP/OFL R strains
- GAT is associated with SERIOUS glucose imbalance and should NOT be used if MOX S
- In fact GAT has been discontinued COMPLETELY

## When to include/which one...

- Group 4 drugs mixture of actions
  - Prothionamide
  - Ethionamide
  - Cycloserine
  - PAS

## FOURTH – Older 2<sup>nd</sup> line agents

- Generally more side effects & bacteriostatic
- Ethionamide = prothionamide for activity
- If ETH resistance then PRO resistant despite disparate sensitivity results
- ETH/PRO resistant then X-reactivity with INH resistance so also cannot rely on as fully active drug
- CYC + PRO or PAS common combination (check TSH)
- All neurotoxic give high dose PYR

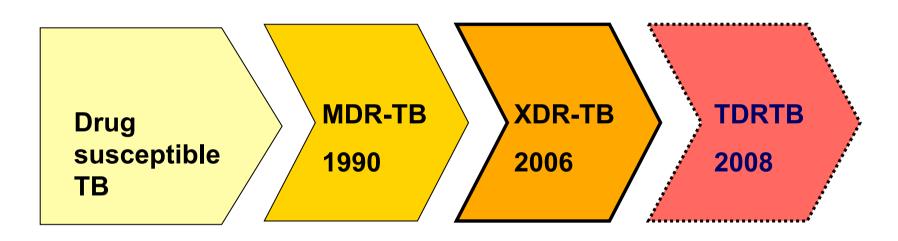
## When to include/which one...

- Group 5 drugs very limited data/poor activity
  - Clofazimine
  - Co-amoxiclav
  - Linezolid
  - Meropenem
  - Clarithromycin

## FIFTH – desperate measures

- Efficacy often uncertain
  - Imipenem/Meropenem
  - Co-Amoxiclav
  - Linezolid
- Or weak and bacteriostatic
  - Clofazamine
  - Azithromycin/clarithromycin
  - Thioacetazone (NOT IN HIV)
- Expensive & may require IV admin
- High-dose INH can be considered if low level R

## Evolution of TB drug resistance



Sensitive

Treatable with 4 drug regimen

Resistance to H&R

Treatable with 2<sup>nd</sup> line drugs

Resistance to 2<sup>nd</sup> line drugs

Treatment options seriously restricted

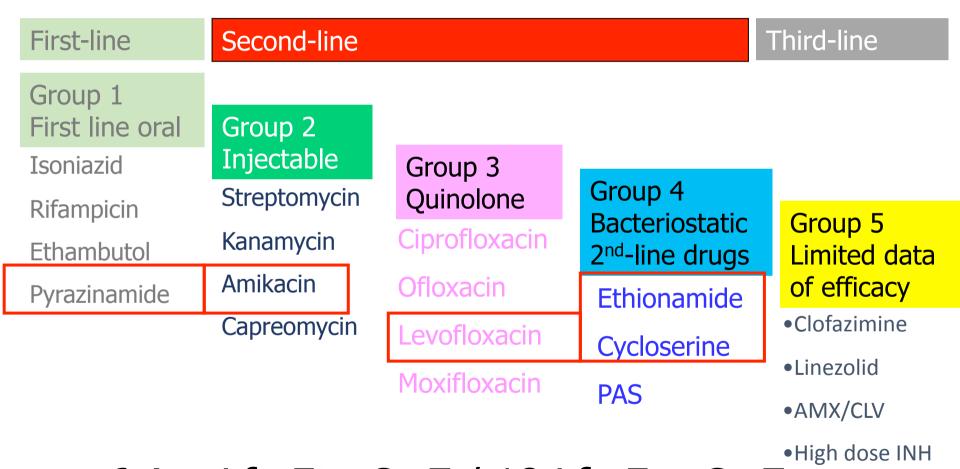
Resistance to all available drugs

No treatment options

# Extensively drug resistant TB (XDR-TB)

- Defined as resistance to:
- At least rifampicin and isoniazid (=MDR) of the first line drugs
- Plus
- Resistance to any fluoroquinolone
- Plus
- Resistance to one or more injectable second line drugs (capreomycin, kanamycin, amikacin)

## Myanmar MDR-TB Regimen



6 Am-Lfx-Eto-Cs-Z / 18 Lfx-Eto-Cs-Z

#### Step 1 Use any available One of One of **PLUS** PLUS these these Begin with any First line agents to Which the isolate is Susceptible Fluoroquinolones First-line drugs Injectable agents Add a Amikacin Pyrazinamide Fluoroquinolone Levofloxacin Capreomycin And an injectable Moxifloxacin Ethambutol Streptomycin Drug based on Ofloxacin susceptibilities Kanamycin

### Step 1

Begin with any First line agents to Which the isolate is Susceptible

Add a
Fluoroquinolone
And an injectable
Drug based on
susceptibilities

Use any available

PLUS

One of these

PLUS

One of these

#### First-line drugs

Pyrazinamide Ethambutol

#### Fluoroquinolones

Levofloxacin Moxifloxacin Ofloxacin

#### Injectable agents

Amikacin Capreomycin Streptomycin Kanamycin

#### Step 2

Add 2<sup>nd</sup> line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

#### Pick one or more of these

#### Oral second line drugs

Cycloserine Ethionamide/ prothionamide PAS



#### Step 1

Begin with any First line agents to Which the isolate is Susceptible

Add a
Fluoroquinolone
And an injectable
Drug based on
susceptibilities

Use any available

**PLUS** 

One of these

PLUS

One of these

#### First-line drugs

Pyrazinamide

Ethambutol

#### Fluoroquinolones

Levofloxacin Moxifloxacin Ofloxacin

#### Injectable agents

Amikacin Capreomycin Streptomycin Kanamycin

#### Step 2

Add 2<sup>nd</sup> line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

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#### Oral second line drugs

Cycloserine Ethionamide PAS



#### Step 3

If there are not 4-6 drugs available consider 3<sup>rd</sup> line in consult with MDRTB experts

#### Consider use of these

#### Third line drugs

Imipenem Linezolid Macrolides Amoxicillin/Clavulanic A High-dose INH Meropenem Clofazamine Thiacetazone

BS

#### Step 3

If there are not 4-6 drugs available consider 3<sup>rd</sup> line in consult with MDRTB experts

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#### Third line drugs

Imipenem Linezolid Macrolides Amoxicillin/Clavulanic A High-dose INH Meropenem Clofazamine Thiacetazone

### Step 4

**HELP** 

#### Consider use of these

#### Expanded access drugs

TMC 207 – weekly dosing OPC-67683 – faster TB clearance than INH/EMB PA-824 – activity against MDRTB

## TDR-TB

## Rich or poor, TDR-TB is a threat to everybody

Over 15.3 half-prepare infected by TB in 2015, and I has four shed so far

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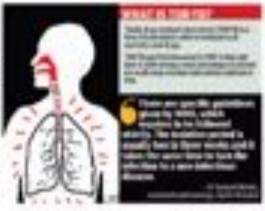
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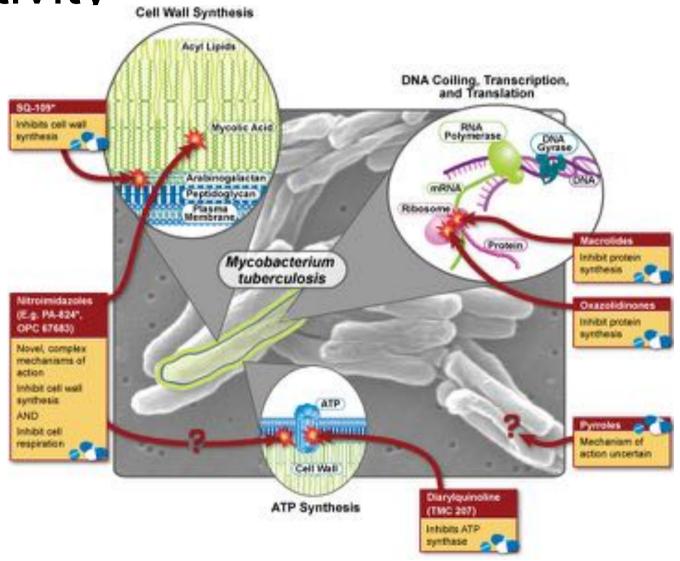
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TB scourge acquires a new dimension: Emergence of Totally Drug-Resistant (TDR) Tuberculosis in India

## TDR-TB

- Resistant to all 2<sup>nd</sup> line drugs
- Culture and smear remain +ve after 18m f 2<sup>nd</sup> line therapy
- Described mainly in India but also elsewhere

New drugs - life cycle and drug activity



## Public Health Law pre - 6 April 2010

- 1984 Act and TB:
- Section 35: compulsory medical examination
- Section 37: power to remove to hospital a person with a notifiable disease
- Section 38: power to detain in hospital a person with a notifiable disease
- Failure to comply leads to a level 1 fine = £100

## Management of



## Thank you

For further information please contact:

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