Management of MDRTB

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HAVE A NICE FLIGHT, SIR.
HA! HE MISSED THE TB.

It began here….

KLINISCHE WOCHENSCHRIFT.

Organ für practische Aerzte.

Mit Berücksichtigung der gesammten Medicinalverwaltung und Medicinalgesetzgebung

unter ständiger Mitwirkung

Redacteure: Professor Dr. C. A. Ewald

Verlag von August Hirschwald in Berlin

Montag, den 13. April 1891. № 15. Achtundzwanzigster Jahrgang

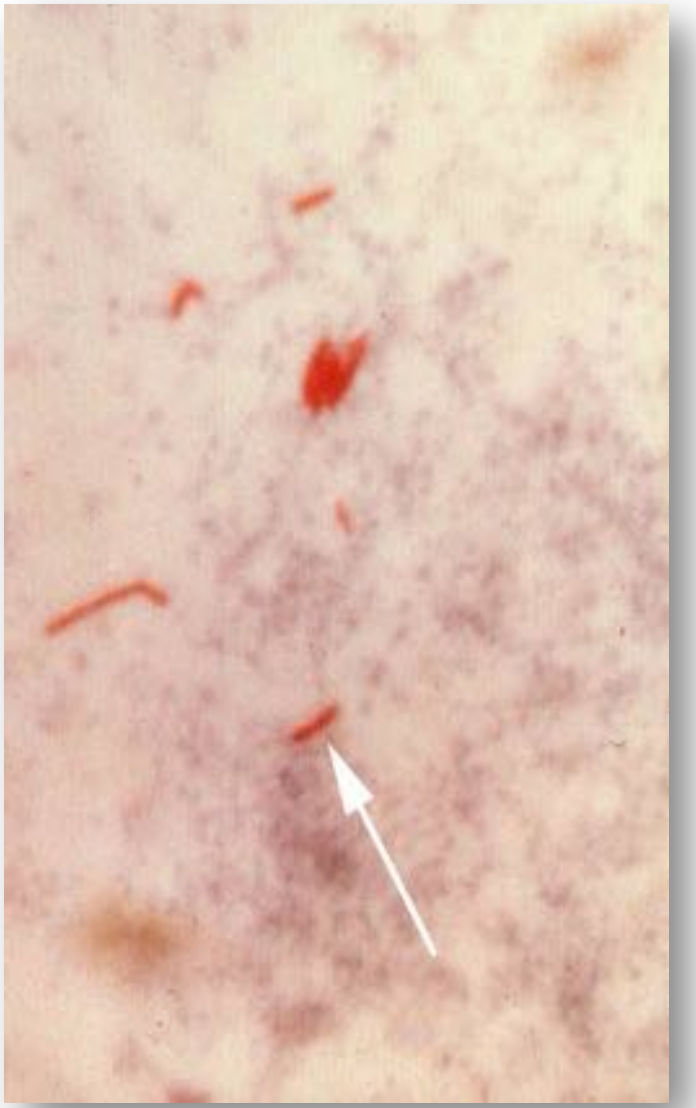
I. Die ätiologische Bedeutung der Tuberculose.

(Nach einem in der physiologischen Gesellschaft zu Berlin am 13. März 91 gehaltenen Vortrage.)

Von

Dr. Robert Koch,

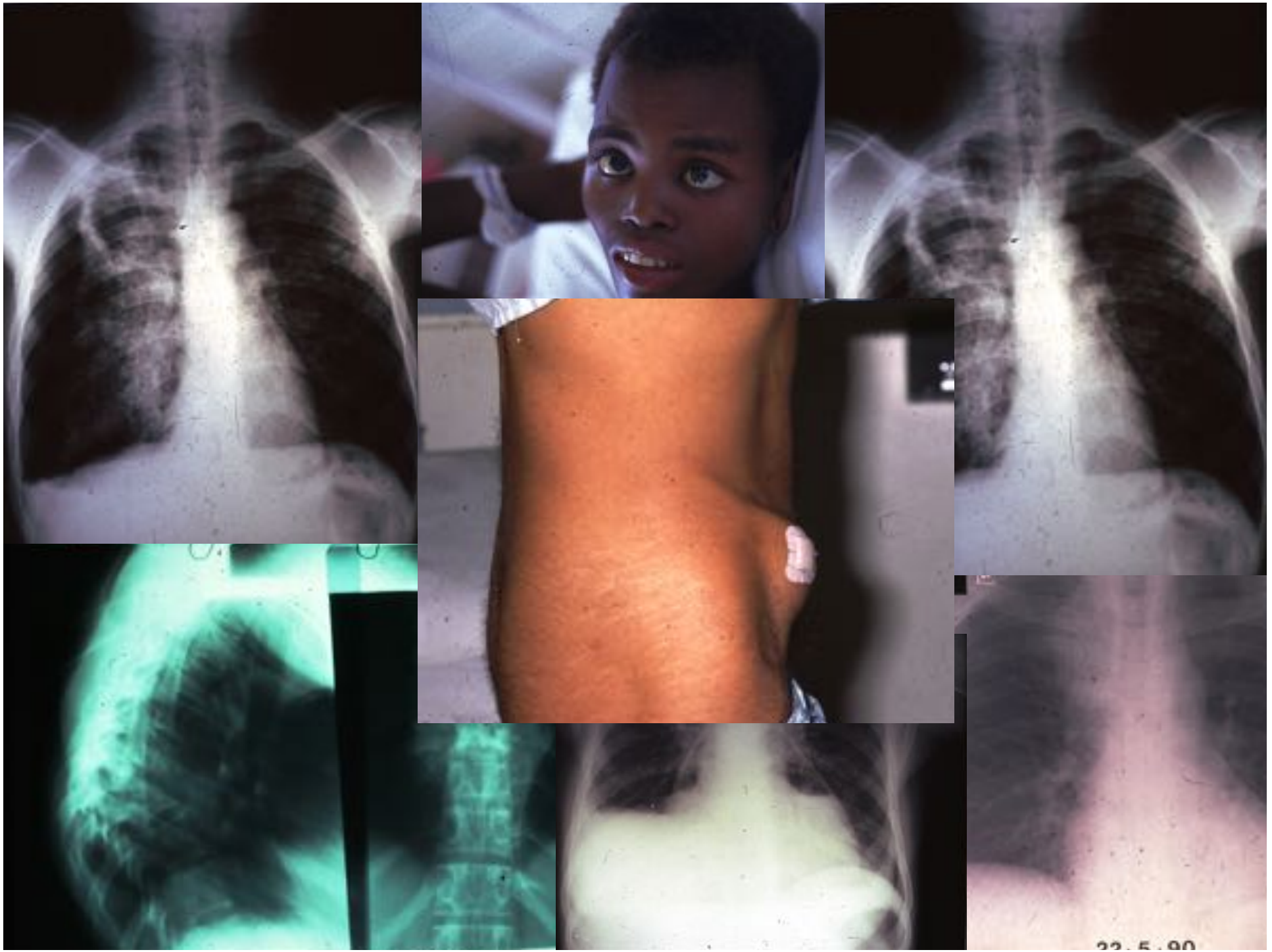
Regierungsrath im Kaiserl. Gesundheitsamte.



Management strategies evolved..

And evolved

Till now…



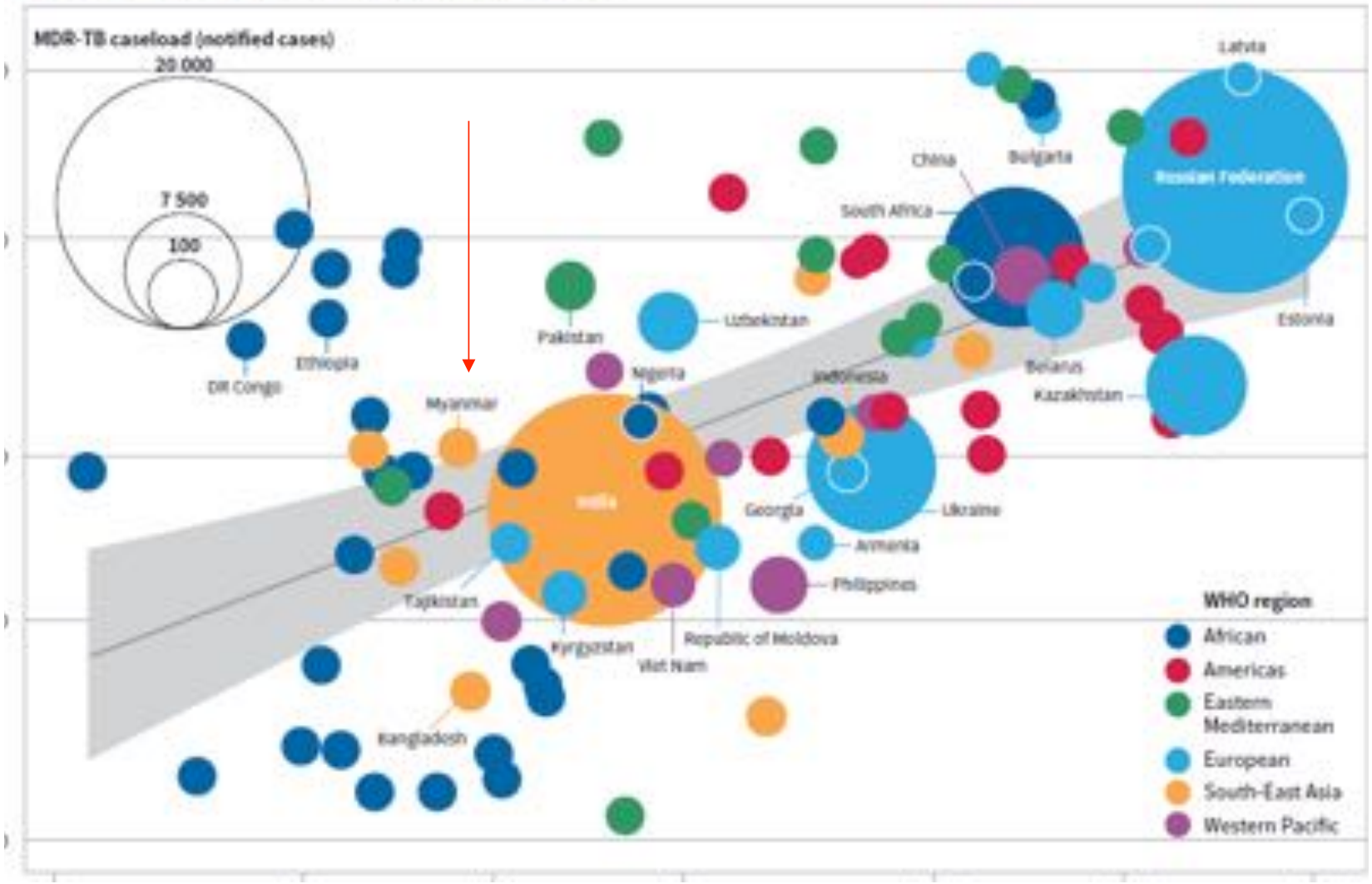
Today

- 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
- Eastern European and central Asian countries have the highest levels of MDR-TB
  - Primary TB - an estimated 35%
  - Secondary TB - an estimated 75%

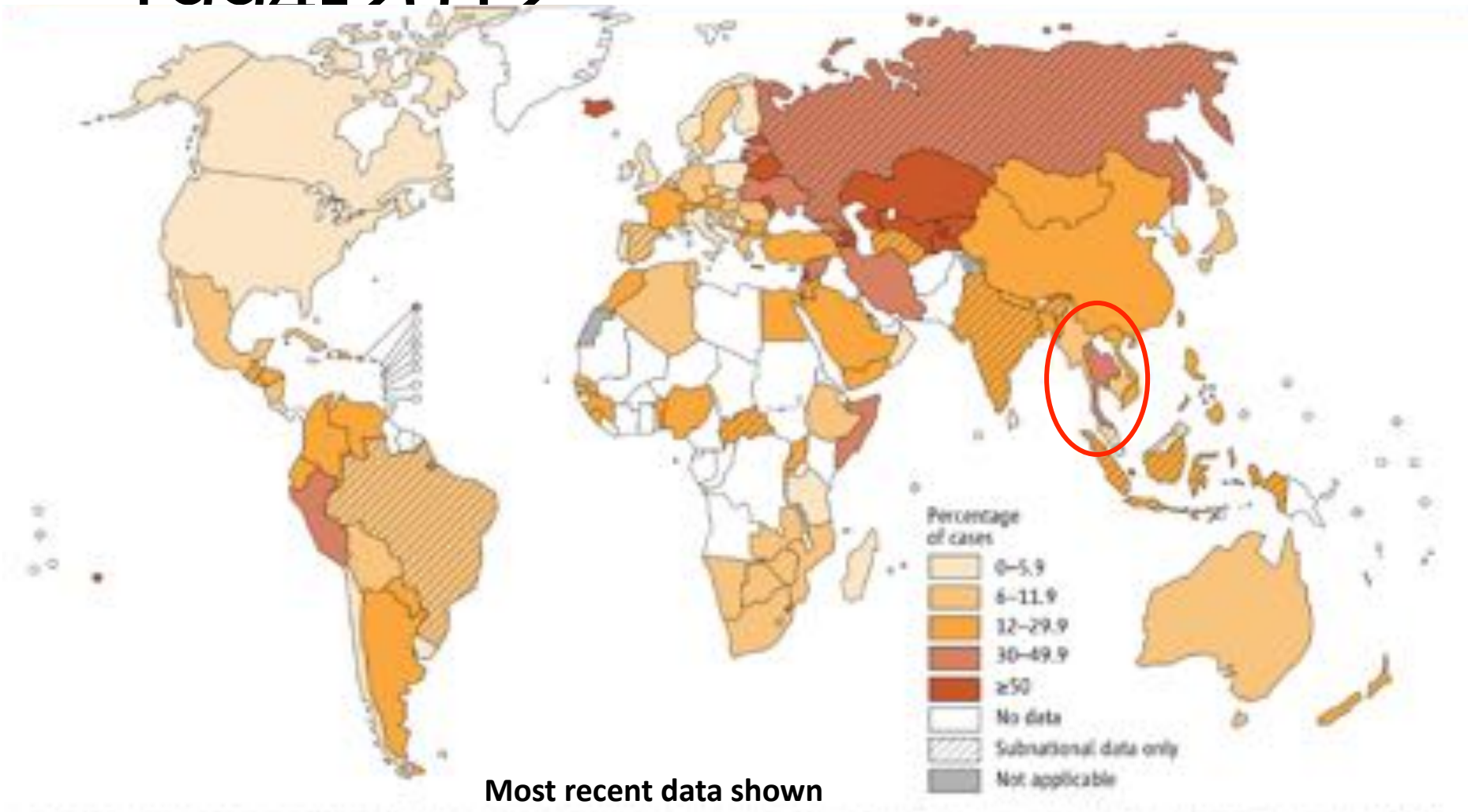
Epidemic of MDRTB



Percentage of new cases with MDRTB 1994-2012

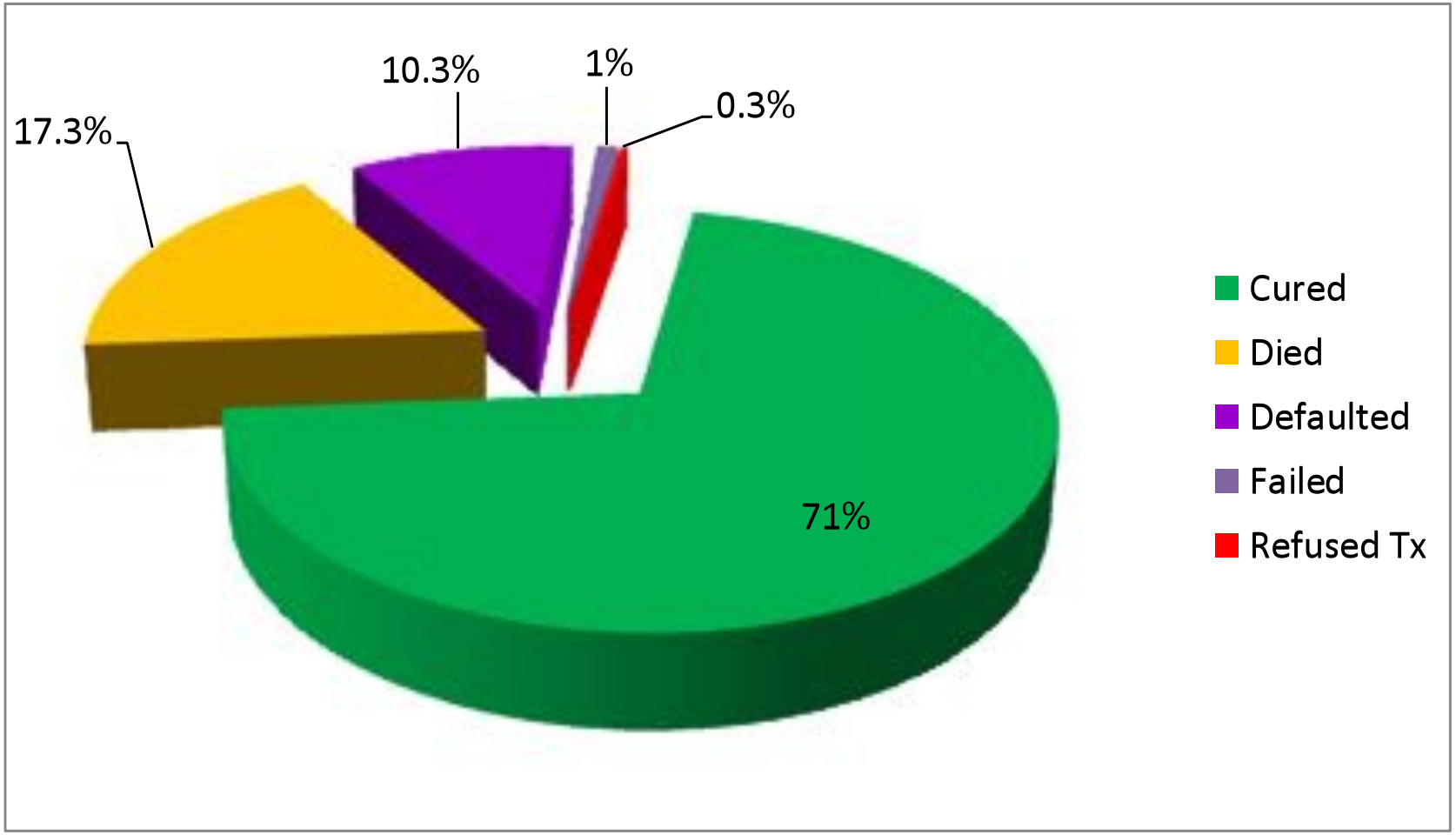
Most recent data shown

Percentage of previously treated TB cases with MDRTB 1994-2012



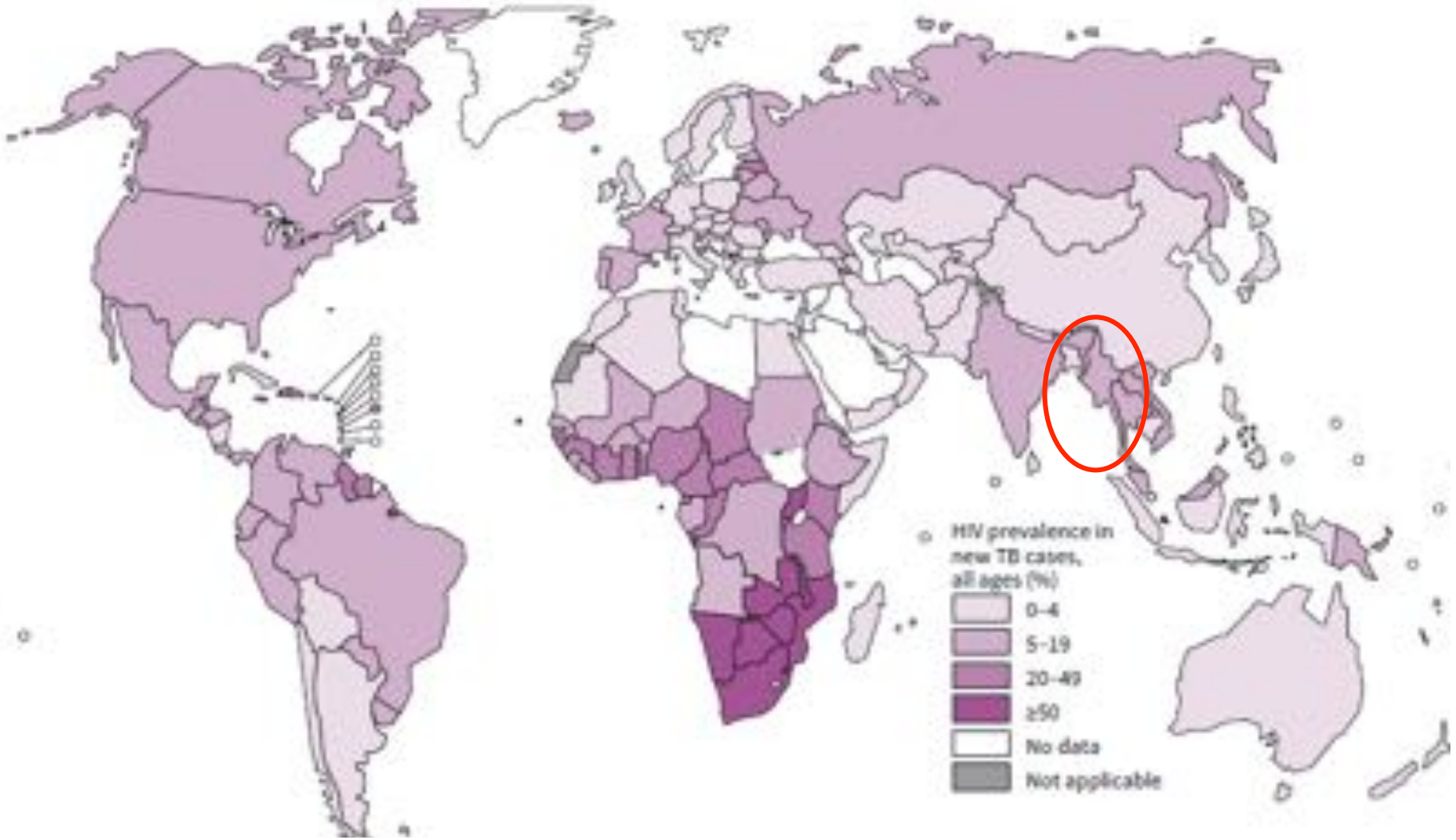
Most recent data shown

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

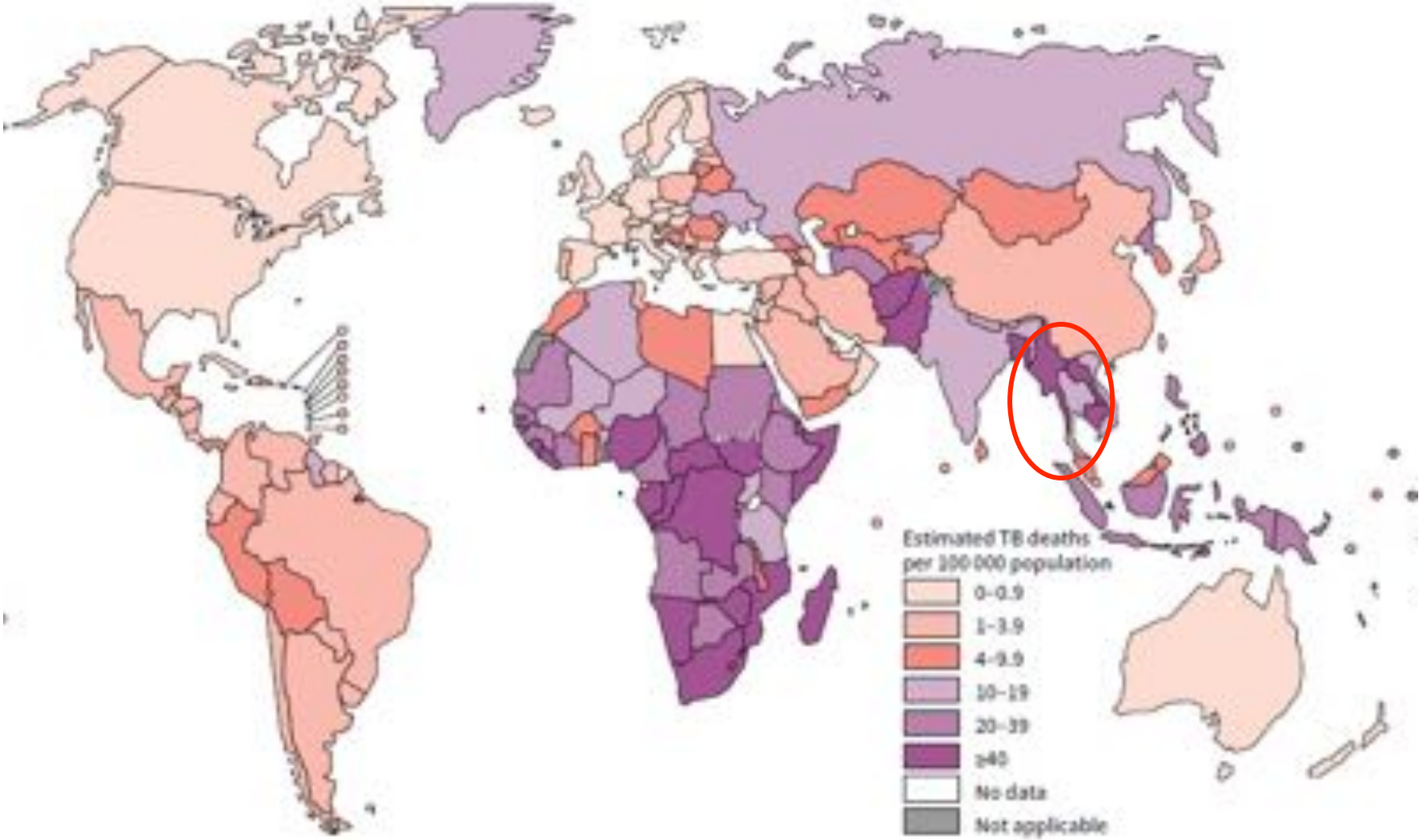


Countries that have notified at least 1 patient of XDRTB by 2012

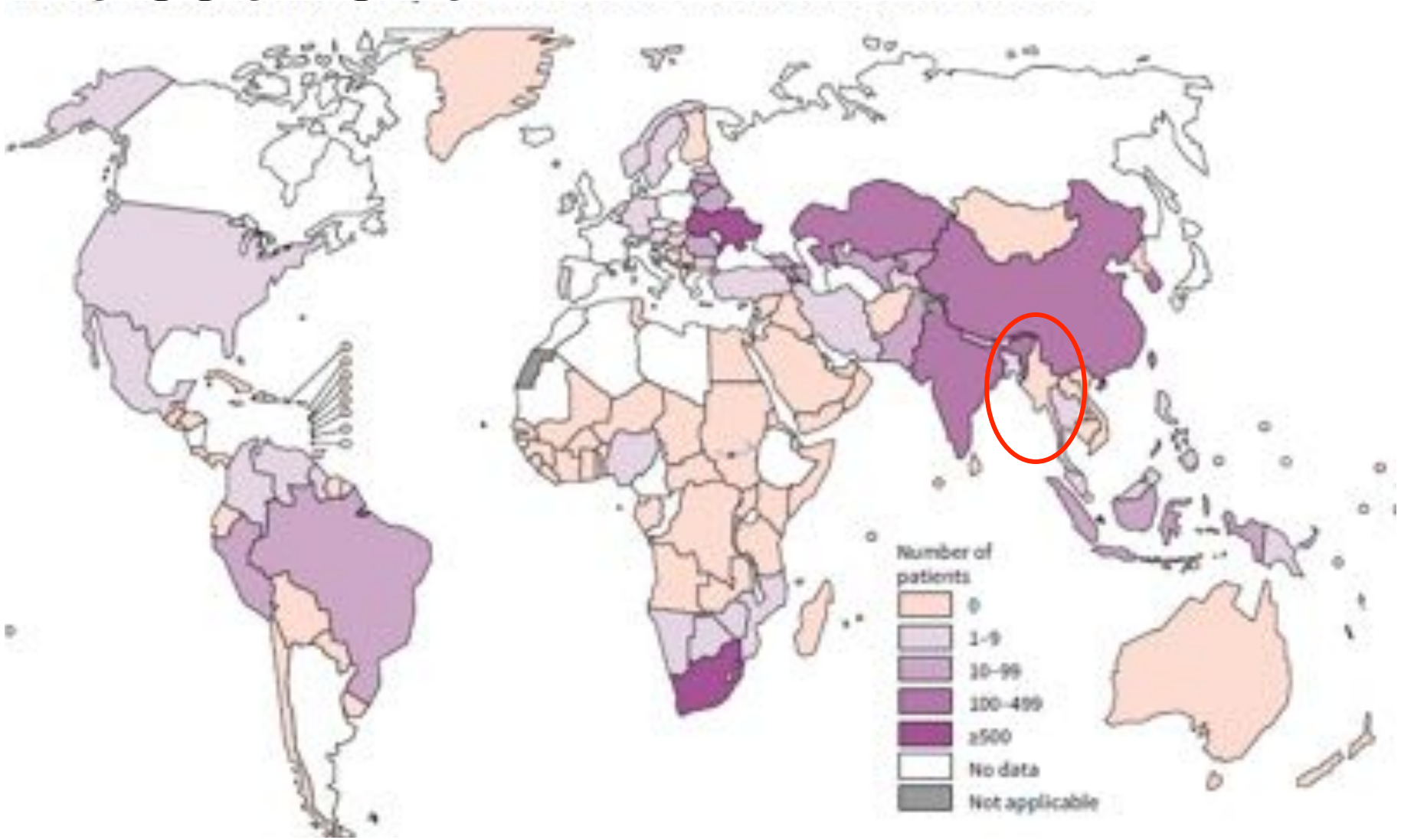
Estimated HIV prevalence in TB



Estimated TB mortality rates in non-HIV TB

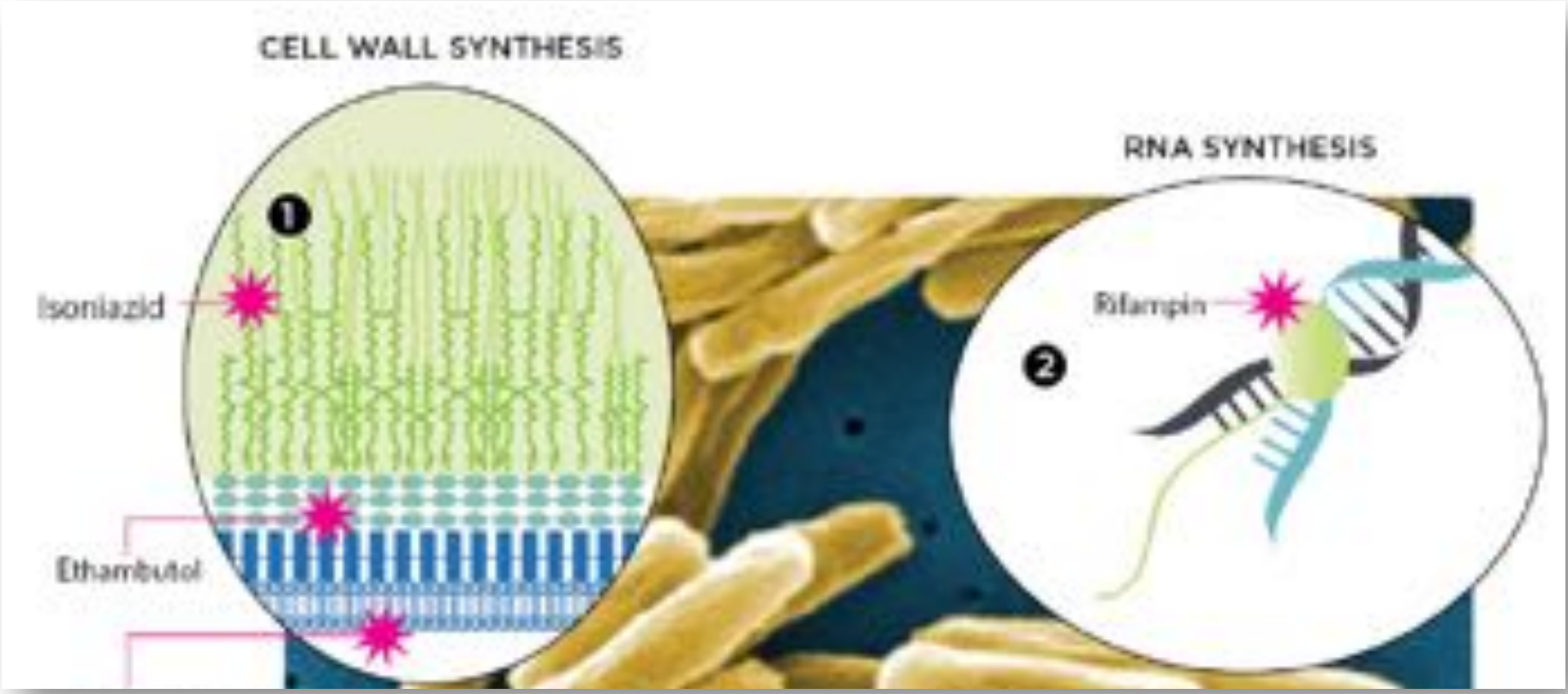


Number of XDRTB started on treatment

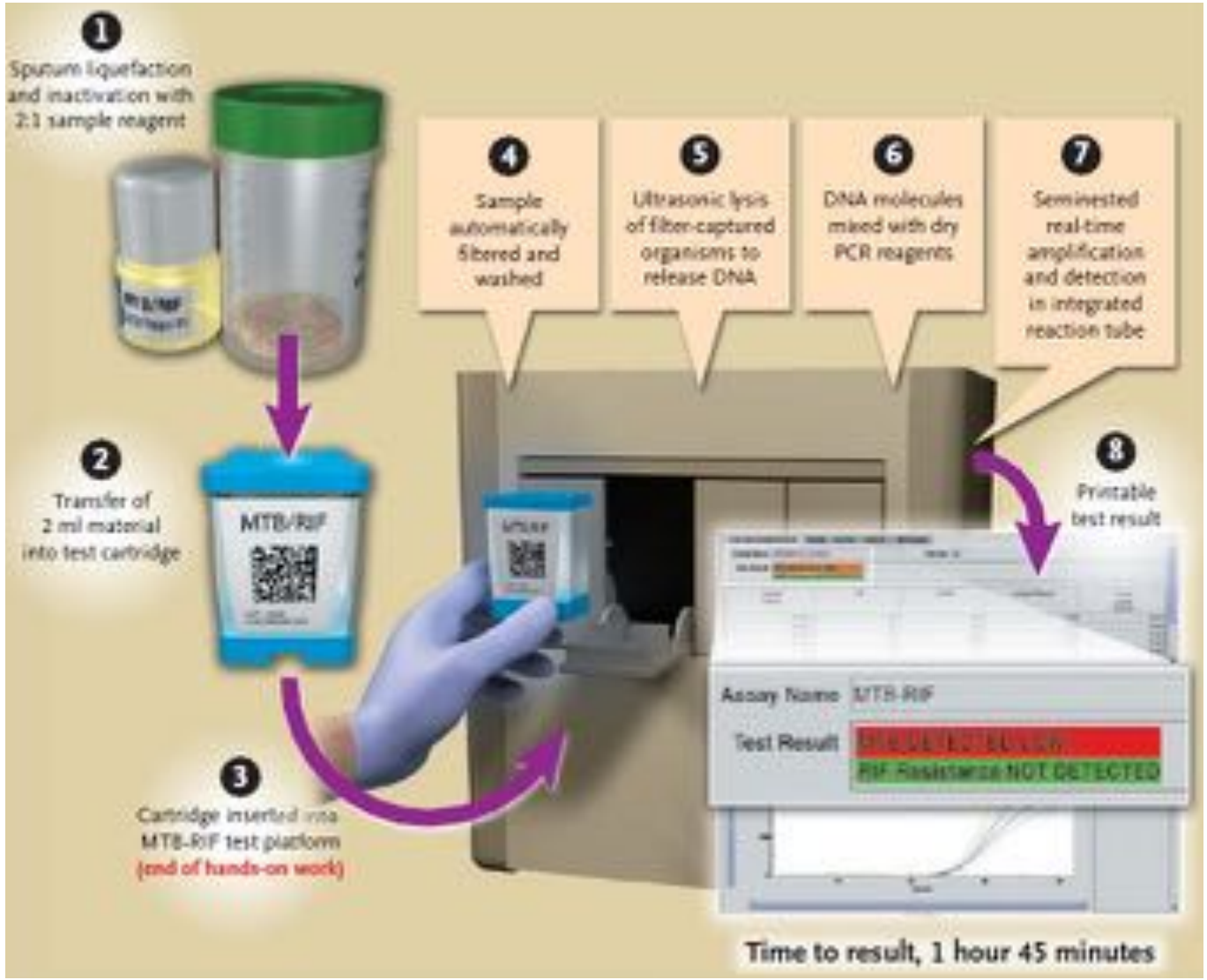


Why has MDRTB occurred?

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 - 1st 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 2nd 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

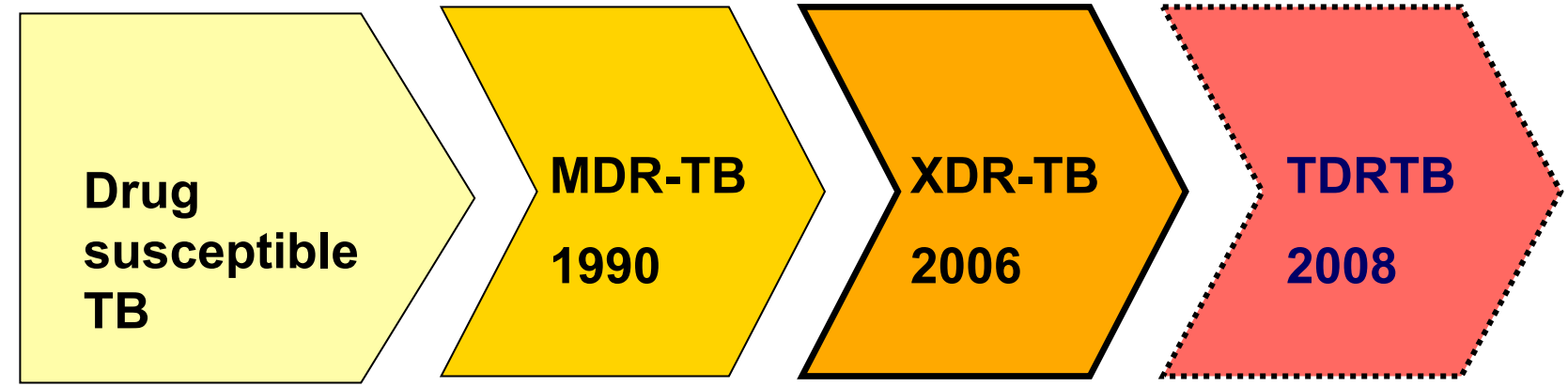
When to include/which one..

- 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

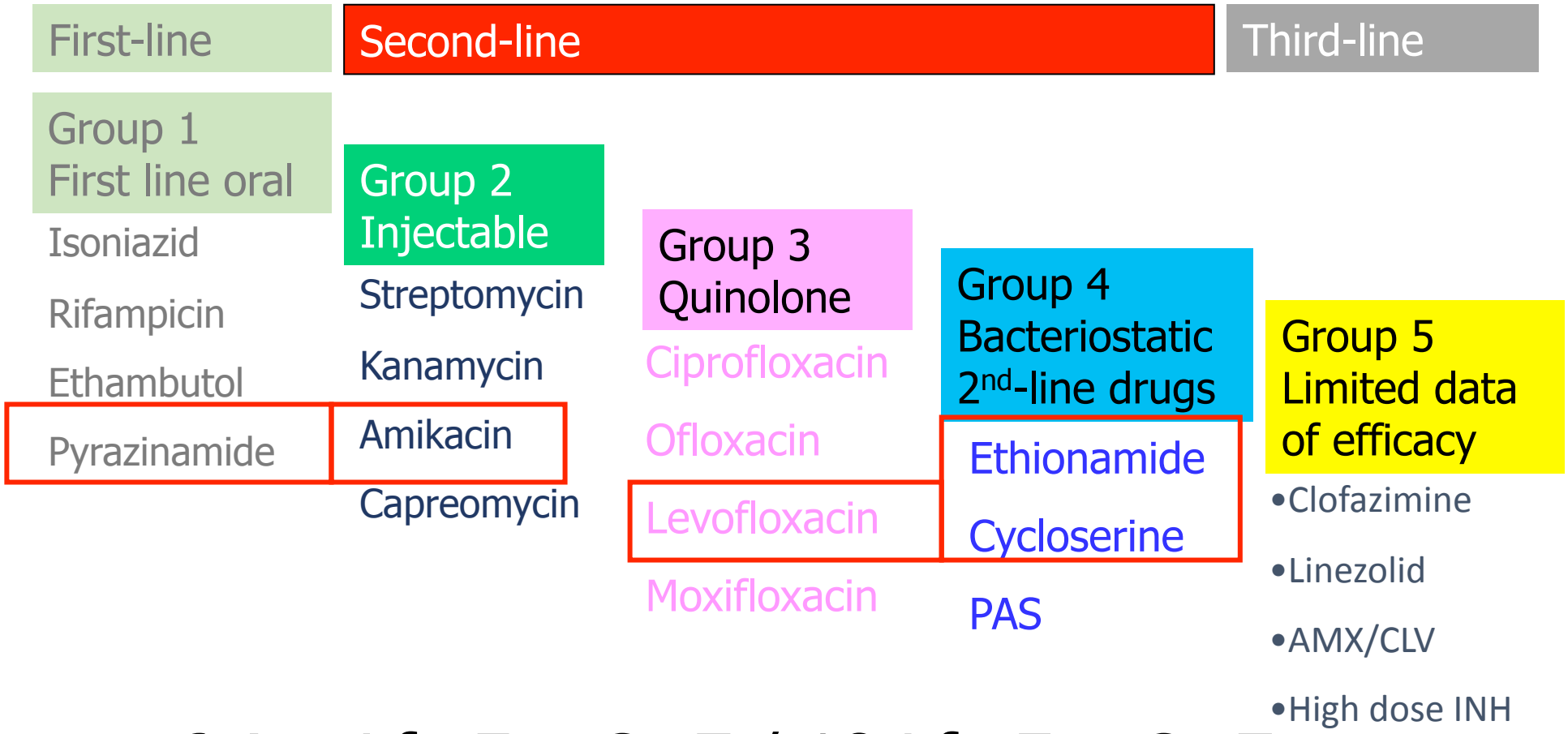


Sensitive	Resistance to H&R	Resistance to 2nd line drugs	Resistance to all available drugs
Treatable with 4 drug regimen	**Treatable with 2nd line drugs**	**Treatment options seriously restricted**	**No treatment options**

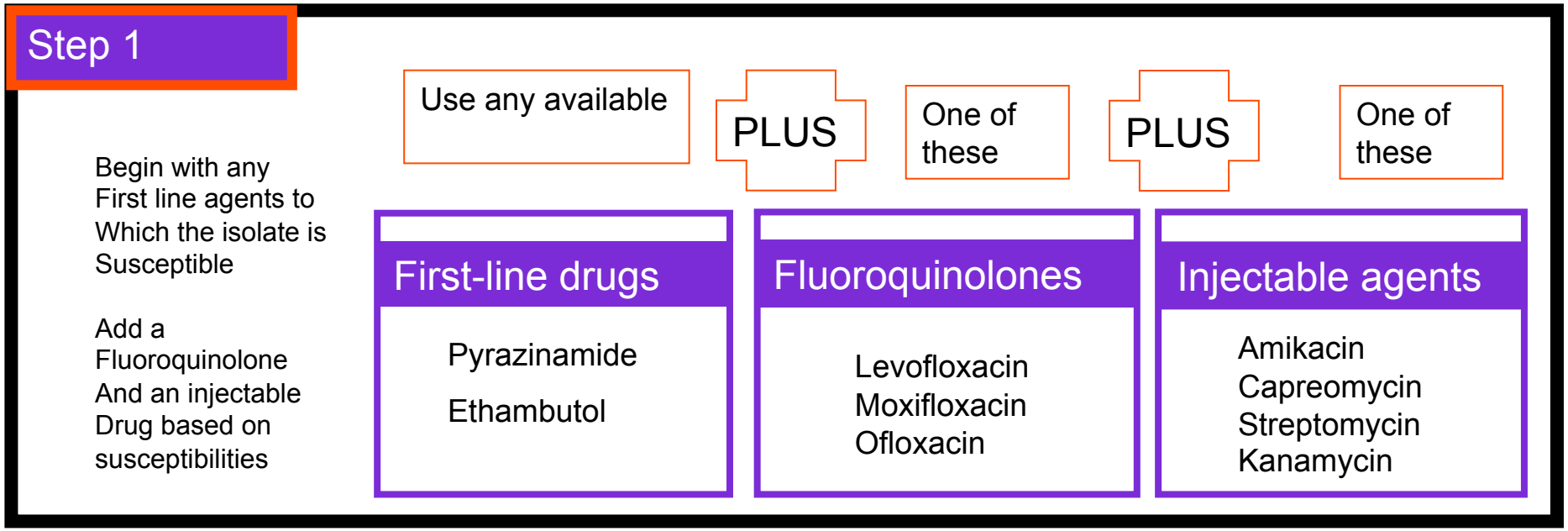
Extensively drug resistant TB (XDR-TB)

- 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
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

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Moxifloxacin
Ofloxacin

Injectable agents

Amikacin
Capreomycin
Streptomycin
Kanamycin

Step 2

Add 2nd 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

PLUS

Step 1

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

Add a Fluoroquinolone And an injectable Drug based on susceptibilities

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Oral second line drugs

Cycloserine
Ethionamide
PAS

PLUS

Step 3

If there are not 4-6 drugs available consider 3rd 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 3rd 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

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

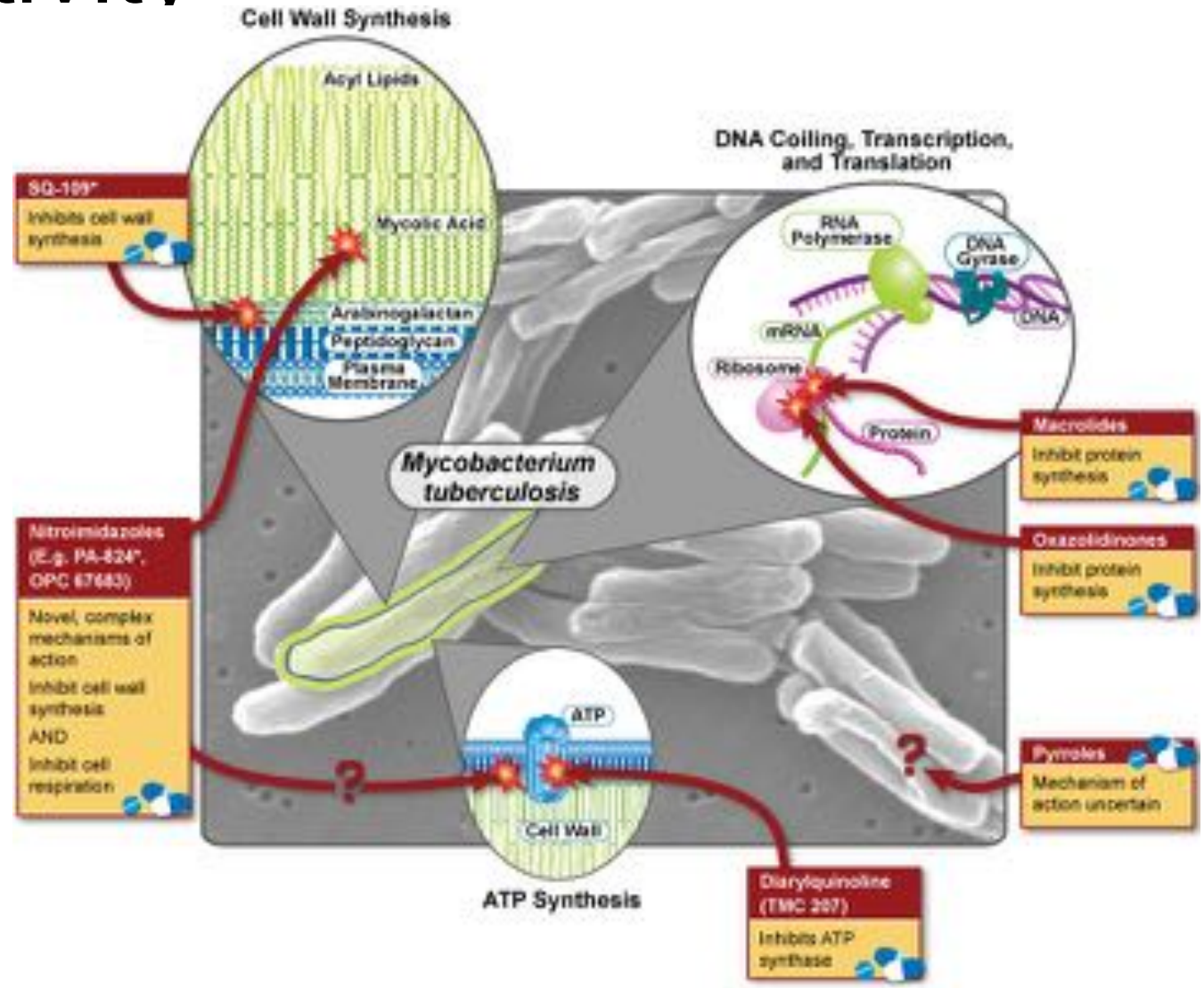
the CALIBRE

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

TDR-TB

- Resistant to all 2nd line drugs
- Culture and smear remain +ve after 18m f 2nd 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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