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Management of Drug-resistant Tuberculosis (DR-TB)

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October 14th, 2008

Tropical Medicine in the –Omics Era

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What the doctor should know about TB and allied diseases

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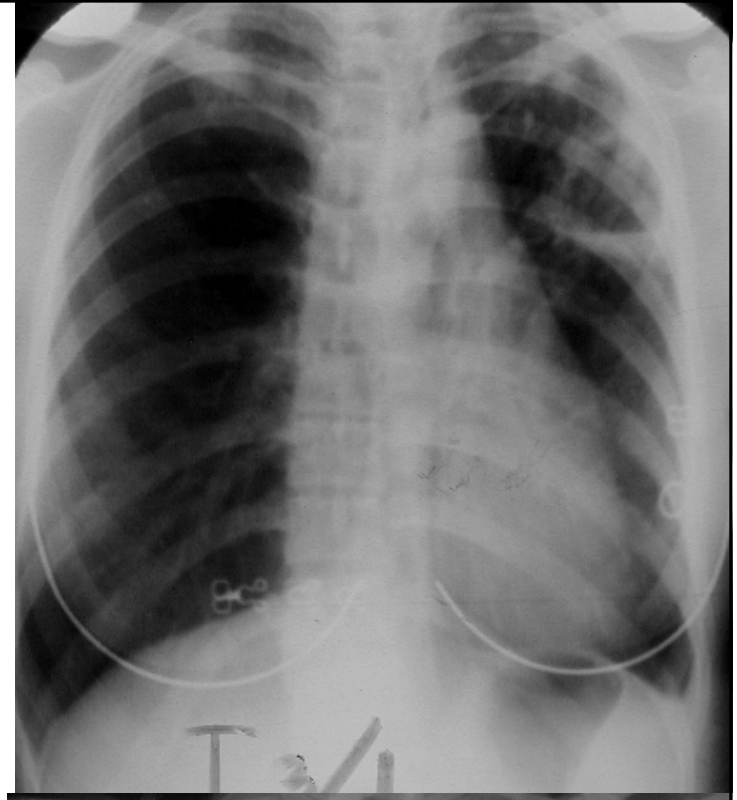
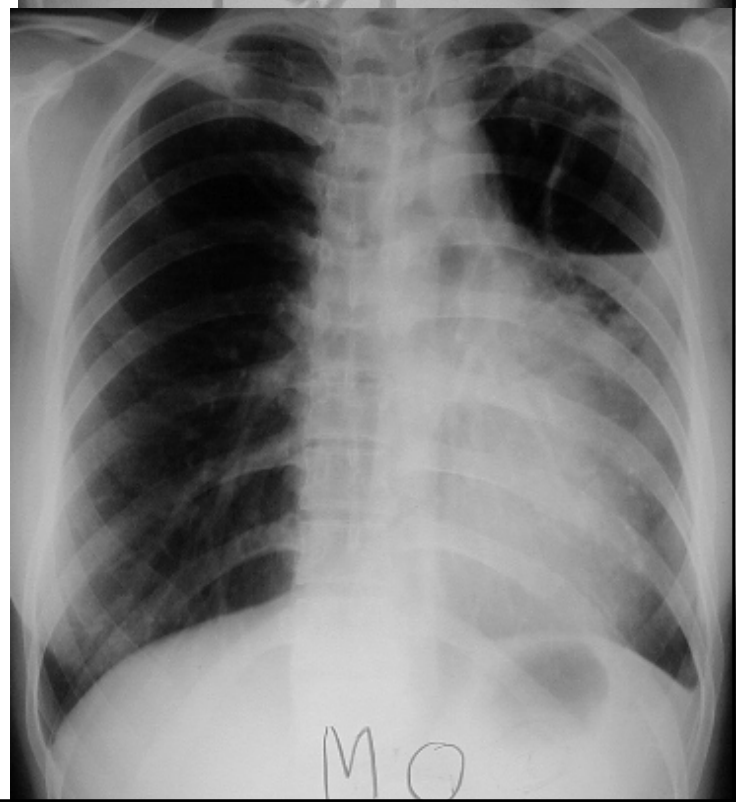
A 50-year-old woman, DM, smear + TB, had persistent positive smears until 5 months after SSCC, with also worsening of symptoms and CXR. Initial response to empirical MDR-TB regimen and then failure at 6 months.

1. Individualized regimen according to DST, with at least 4 new drugs
2. Adjunctive surgical lung resection
3. Adjunctive interferon-gamma
4. Artificial pneumothorax
5. Suppressive dose of INH





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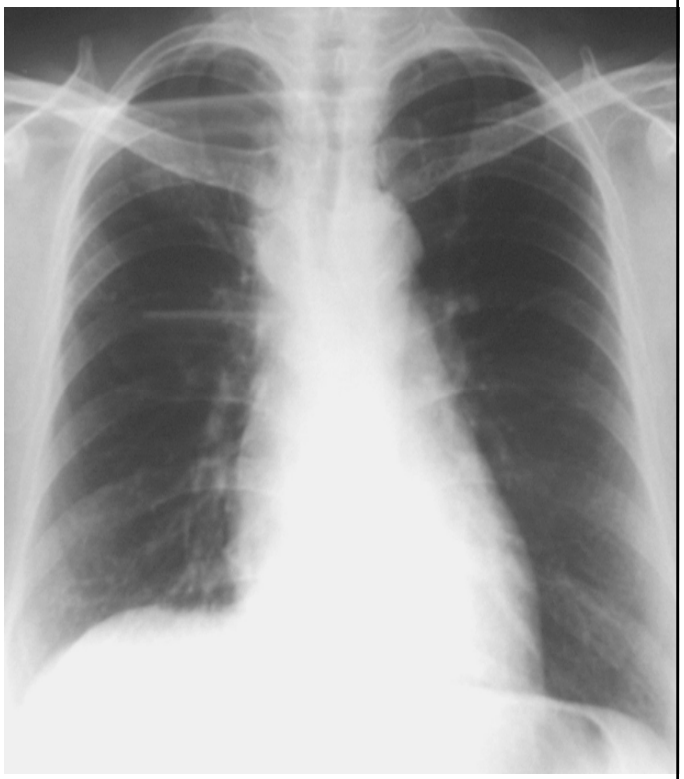
A 60-year-old man, previously healthy referred for treatment of MDR-TB. He received Category II treatment for 4 months with 5-kg weight gain and scanty cough. His CXR was markedly improved with few residual scarring, but smears were persistently positive. Initial DST revealed MDR-TB.

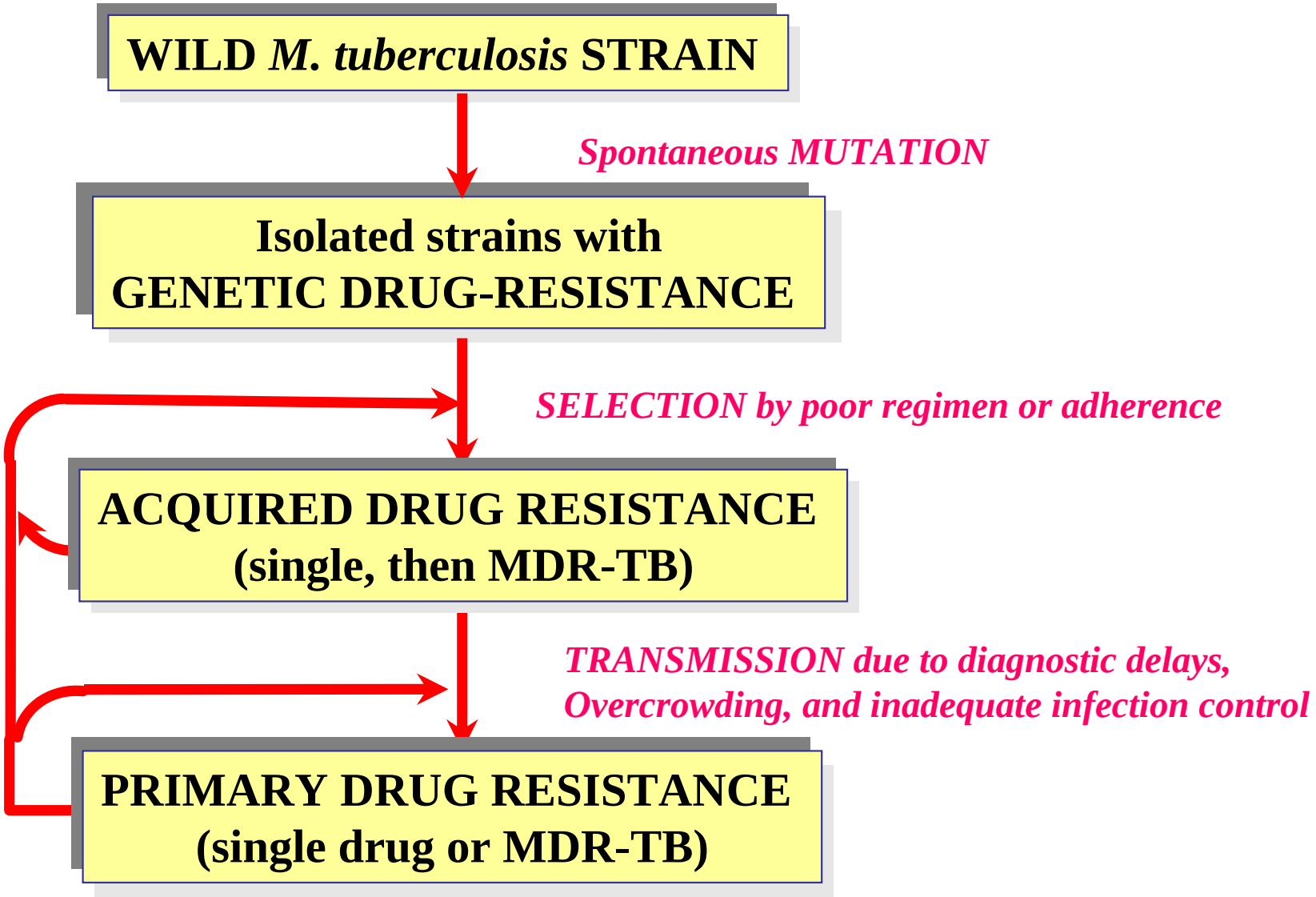


1. Disconcordance between in vitro DST and in vivo response
2. True MDR-TB
3. Specimen mislabeling
4. Laboratory cross contamination
5. NTM colonization

Definition of Drug Resistant TB

- Mono-resistance : infecting isolates of *M. tuberculosis* are confirmed to be resistant in vitro to one first-line antituberculosis drug
- Poly-resistance : resists to more than one first-line
- Multidrug-resistance : resists to at least isoniazid and rifampicin
- Categorize clinically into drug resistance in those never received treatment or previously treated

How Does Drug-Resistant TB Develop?



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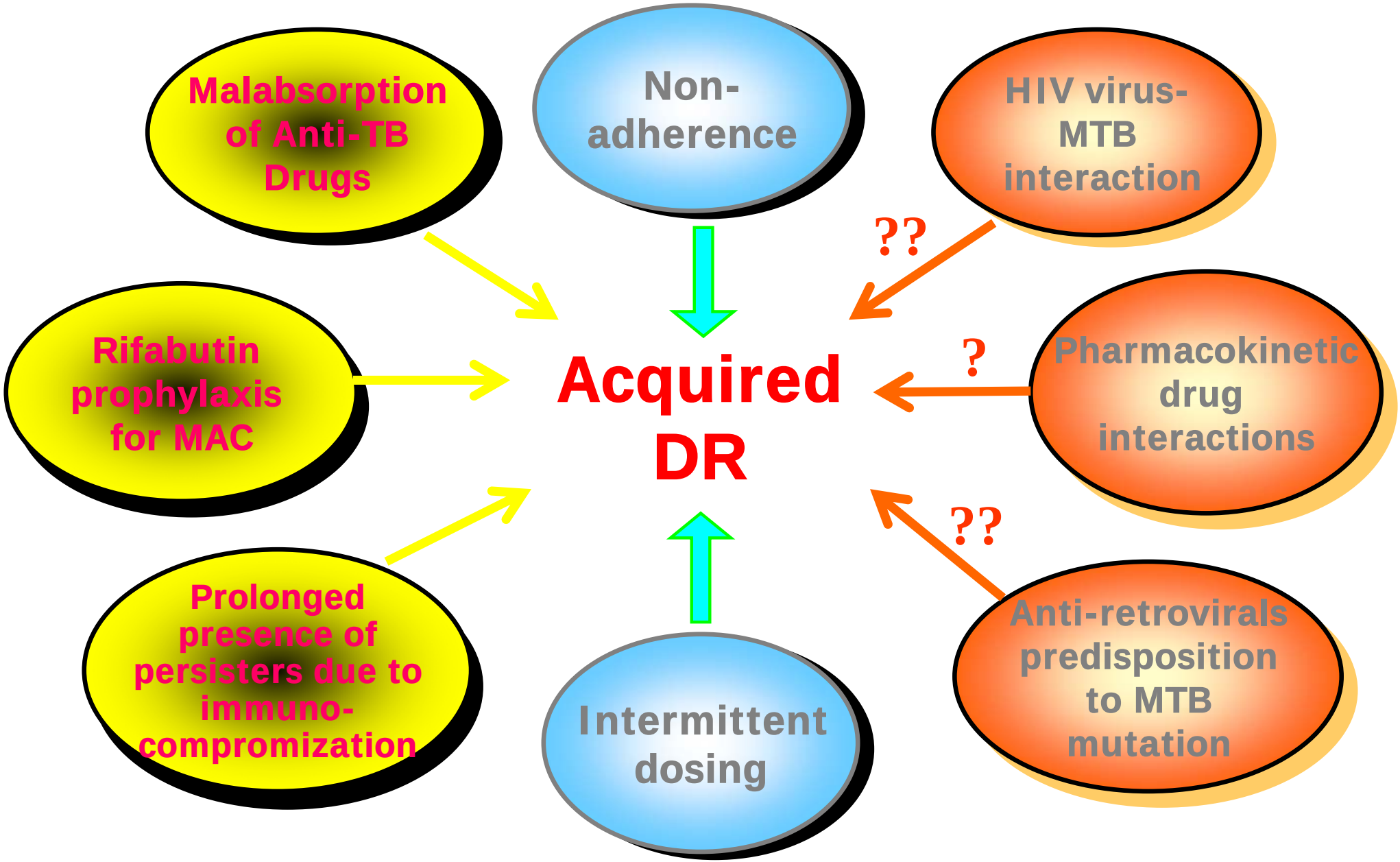
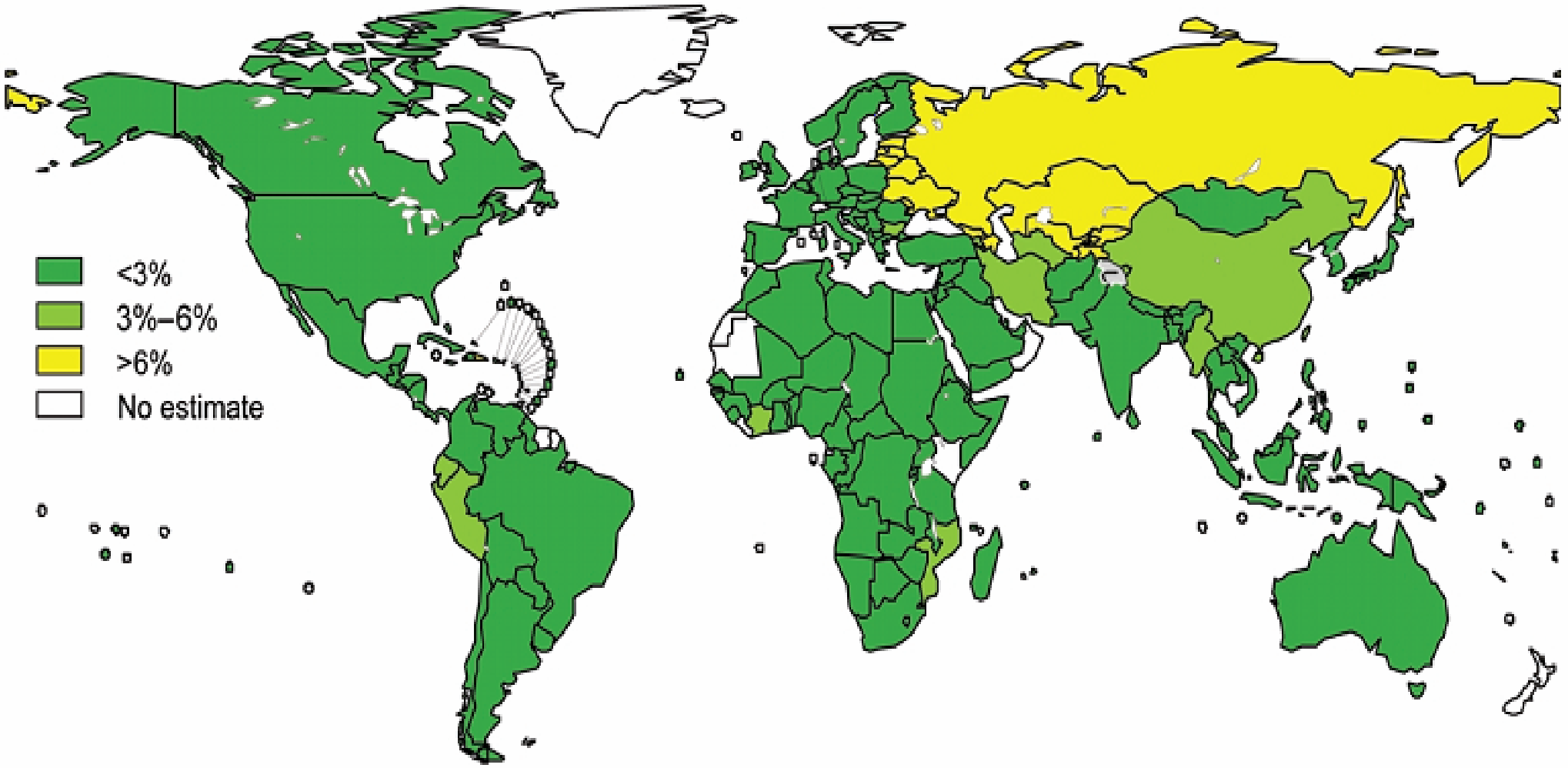
Prevalence of DR-TB in Thailand

Year	Area	No.	Type	H	R	E	S	MDR-TB
1998	46 provinces	1,137	Initial	12.3	5.6	7.2	11.6	2.02
1998	Chiang Rai	1,077	Initial	13.2	10.8	5.8	15.6	6.3
1998	Chiang Rai		Acquired	44.4	42.4	19.2	37.7	33.8

HIV and Acquired DR



Global Prevalence of MDR-TB Among New Cases, 2004 (median prevalence 1.2 %, 0 -14.2 %)



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Global Prevalence of MDR-TB Among Previously Treated Cases, 2004 (median prevalence 7.7, 0-58.3 %)

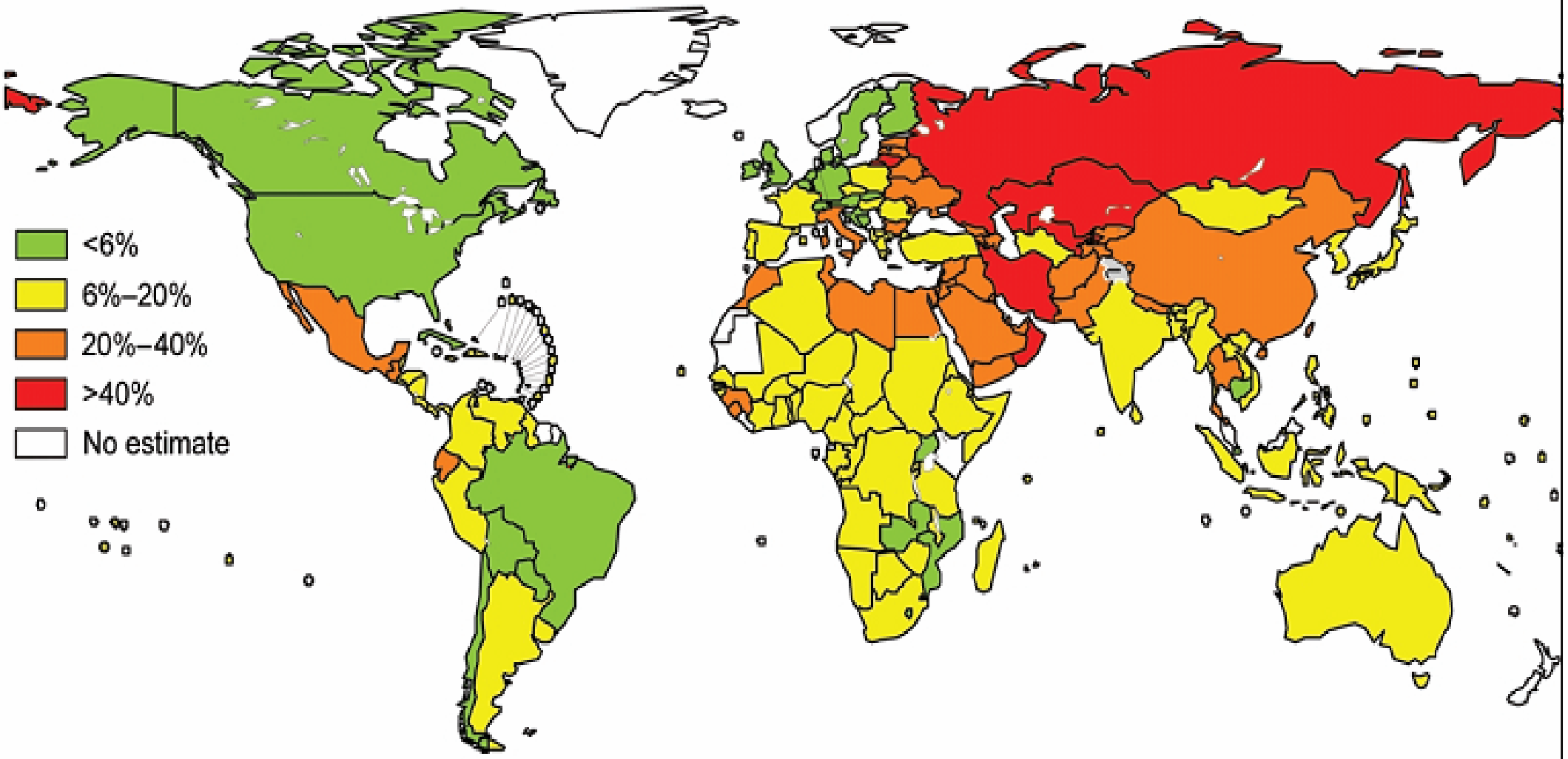

TABLE 1.1 **Causes of inadequate antituberculosis treatment** (1)

HEALTH-CARE PROVIDERS: INADEQUATE REGIMENS	DRUGS: INADEQUATE SUPPLY/QUALITY	PATIENTS: INADEQUATE DRUG INTAKE
Inappropriate guidelines	Poor quality	Poor adherence (or poor DOT)
Noncompliance with guidelines	Unavailability of certain drugs (stock-outs or delivery disruptions)	Lack of information
Absence of guidelines	Poor storage conditions	Lack of money (no treatment available free of charge)
Poor training	Wrong dose or combination	Lack of transportation
No monitoring of treatment		Adverse effects
Poorly organized or funded TB control programmes		Social barriers
		Malabsorption
		Substance dependency disorders

WHO. Guidelines for the programmatic management of drug-resistant tuberculosis, 2006

Previously Treated TB Patients

- Probability of any resistance was over 4-fold higher and 10-fold for MDR-TB
- In some countries, retreatment cases accounted for more than 20 % of sputum smear-positive cases
- Globally, one third of MDR-TB cases had resistance to all 4 first-line drugs
- MDR-TB patients often live for several years before succumb to the disease

Categorization for Retreatment

- Relapse: previously complete or cure
- Default: interrupt for > 2 months after treated for > 1 months
- Failure:
  - Initial smear+ : persistent at 5 months, clinical and radiological not improved
  - Initial smear- : converted to positive at 2 months, clinical and radiological not improved, culture proven

Standardized Retreatment Regimen

- Smear-positive cases, drug susceptibility testing (DST) if available
- Category II (2 SHRZE + 1 HRZE + 5 HRE) for all (failure, default, relapse)
- Over all success rate is 60 % (80 % for relapse-default, 0-40 % for failure)
- Consideration
  - Prevalence of MDR-TB
  - Availability of laboratory for DST
  - System for containment

Managing Retreatment Cases

- Relapse
  - Category I if complete or cure under DOT
  - Category II if not
- Default: Category II
- Failure: Category IV
  - Standardized
  - Standardized + individualized
  - Empirical + individualized

More aggressive in those impaired immunity, poor respiratory reserved, life-threatening

Regimen Design for MDR-TB

- At least 4 drugs which either certain or almost certain effectiveness
- Once-a-day dosing except for Eto, Cs, PAS, at least 6 days a week
- An injectable agent is used for a minimum of 6 months and remains persistent negative smear or culture
- Minimum duration of 18 months beyond culture conversion, under directly observed therapy (DOT)
- Pyrazinamide can be used for the entire treatment

WHO. Guidelines for the programmatic management of drug-resistant tuberculosis, 2006

SLD Susceptibilities of Thai MDR-TB 99 Isolates (2001-2002)

Drugs	% Susceptible
Amikacin / Kanamycin	95
Ofloxacin / Ciprofloxacin	91
Para-aminosalicylic acid	85
Ethionamide	78
Clarithromycin	8

Prammananan T, et al. Int J Tuberc Lung Dis 2005; 9:216-9

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Outcome Evaluation

Cured. A Category IV patient who has completed treatment according to the programme's protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture[1] is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

Failed. Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered

WHO. Guidelines for the programmatic management of drug-resistant tuberculosis, 2006

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MDR-TB in Siriraj Hospital, 2003-2005

- There were 65 patients, 24 female and 41 male
- Among 53 patients with blood tests, 27 were HIV-positive and 8 had DM
- Among 32 patients with history of TB were disclosed, 3 were new cases
- 28 isolates were tested with second-line anti-TB
  - 25/28 (89 %) were sensitive to amikacin
  - 20/28 (71 %) were sensitive to ofloxacin or ciprofloxacin
  - 9/12 (75%) were sensitive to levofloxacin
  - 20/23 (87 %) were sensitive to moxifloxacin
  - 21/24 (88 %) were sensitive to ethionamide
  - 20/26 (77 %) were sensitive to PAS
  - 11/11 (100 %) were sensitive to linezolid
  - 3/12 (25%) were sensitive to clarithromycin
  - 11/28 (39 %) were sensitive to ethambutol

Patients with MDR-TB
Siriraj Hospital, 2003-2005

- Among 37 patients with outcome evaluation, 14 were cure (1 HIV), 6 were failed (4 non-HIV, 1 HIV, 1 NA), and 17 died (15 HIV)
- Among 54 evaluated CXR, 24 revealed cavity (3 HIV, 7 DM, 13 non, 1 NA) and 30 without cavity (1 DM, 24 HIV, 6 non)

Transmissability of MDR-TB

- 218 close contacts (non-HIV) of 64 MDR-TB cases in Brazil, 2.8 - 4.6 % developed TB in 1 year (4.2 % for drug-susceptible bacilli)

  Kritski AL, et al. Am J Resp Crit Care Med 1996; 153:331-5

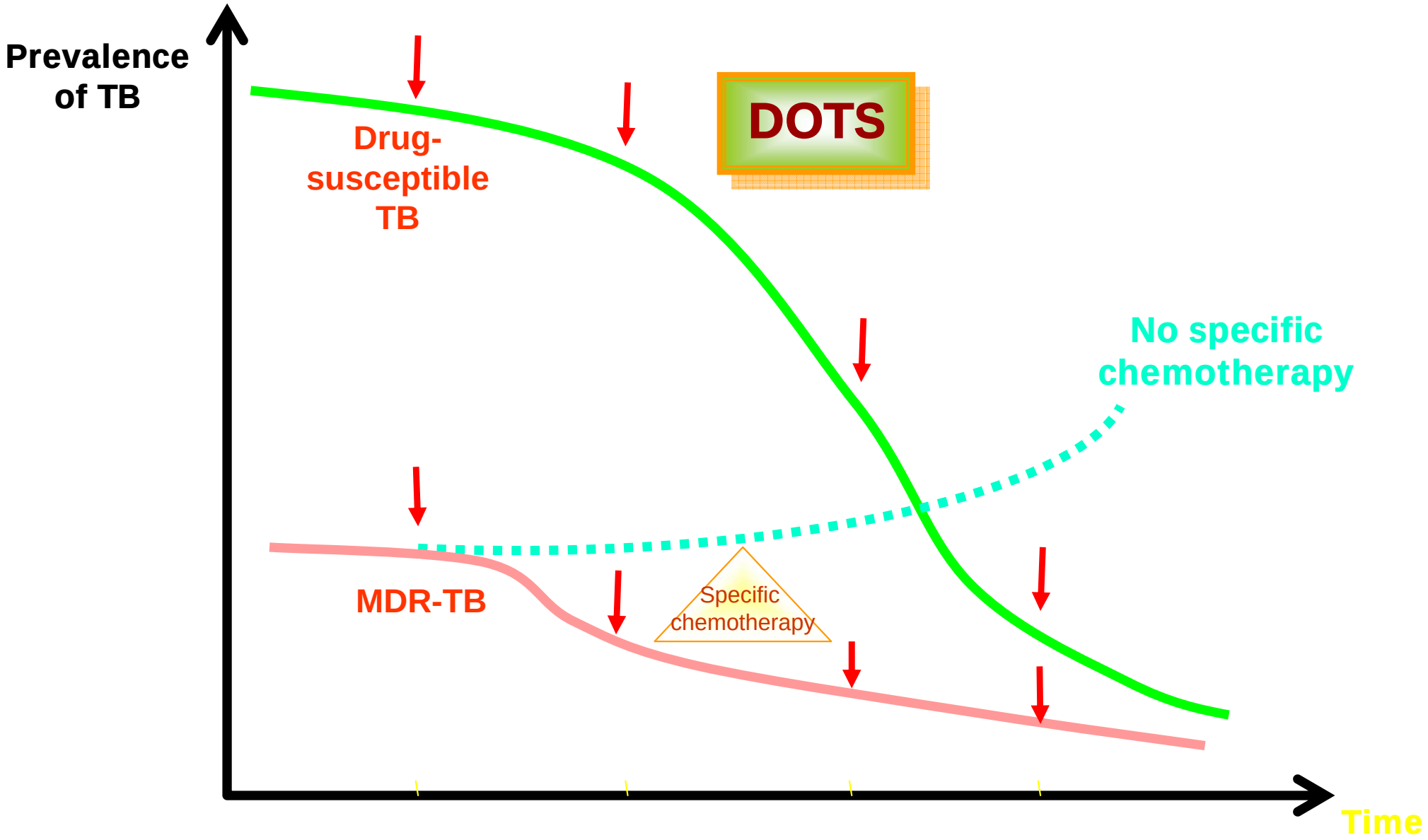
- No clustering from molecular epidemiologic study was found among 25 MDR-TB patients in Mexico

  Garcia-Garcia ML, et al. Arch Intern Med 2000; 160:630-6

- TST conversion in 6 % of 946 contacts of 102 MDR-TB cases in USA, 5 % of the converters developed MDR-TB

  Nitta AT, et al. Am J Resp Crit Care Med 2002; 165:812-7

Combined Chemotherapy Strategy in the Control of Tuberculosis



Yew WW. Treatment of TB in TUBERCULOSIS. Sharma SK (ed) 2nd Edition 2005

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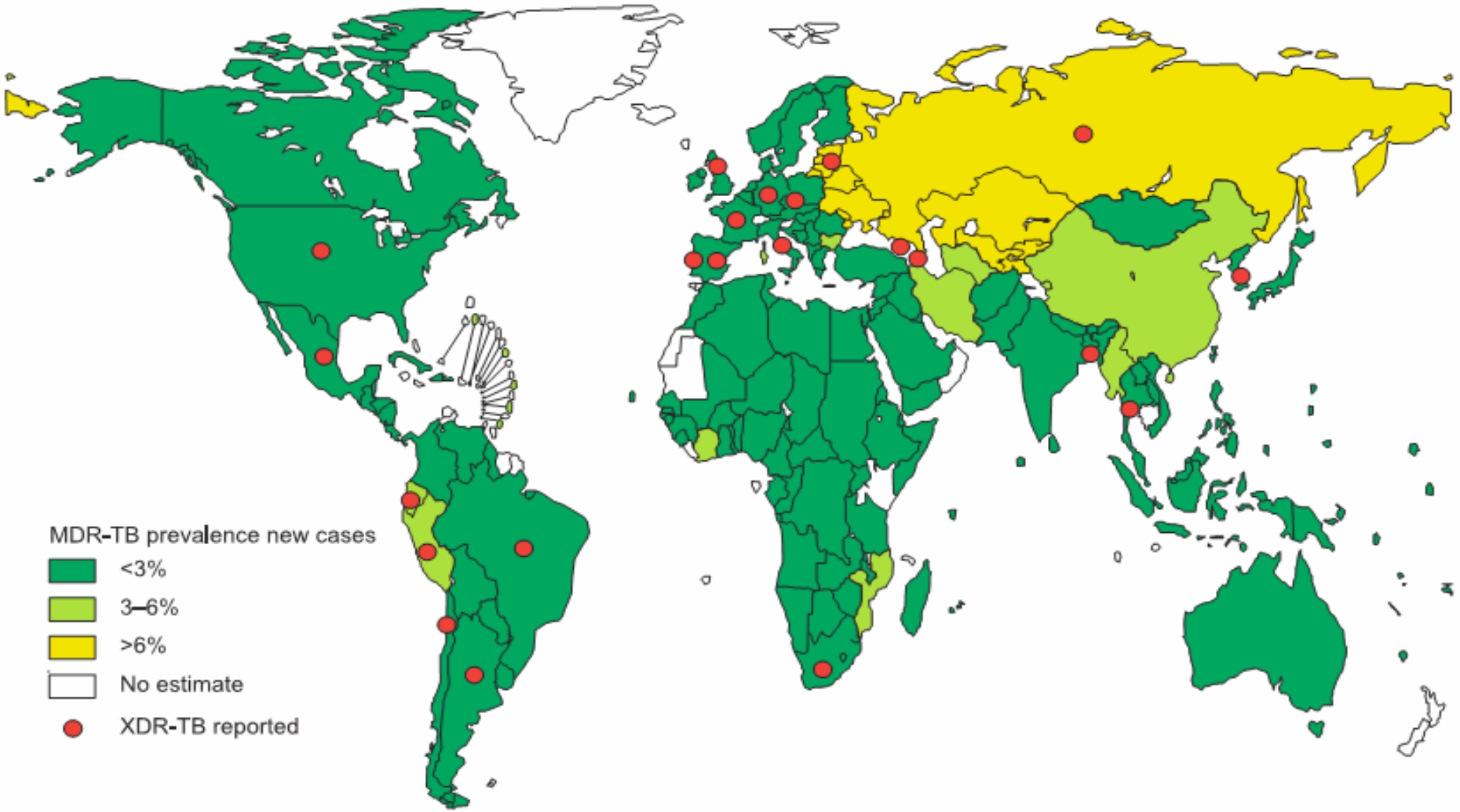
Global Report for XDR-TB, 2004



Extremely Drug Resistant TB

Mycobacterium tuberculosis that is resistant in vitro to at least isoniazid and rifampicin among first-line drugs, and at least three or more of the six main classes of second-line drugs (SLD)

- Aminoglycosides
- Polypeptides
- Fluoroquinolones
- Thioamides
- Cycloserine
- Para-aminosalicylic acid

Shah NS, et al. Int J Tuberc Lung Dis 2005; 9 (Suppl 1):S77

Holtz TH, et al. Int J Tuberc Lung Dis 2005; 9 (Suppl 1):S258

Extensively Drug-resistant (XDR) TB

- In Msinga district. KwaZulu Natal (KZN), South Africa 221/542 isolates during Jan05-March06 were MDR-TB (40.8 %), and 53 (24 %) were X2DR-TB
- 52 patients died with a median survival after sputum collection of only 16 days (70 % in 30 days)
- HIV were positive in all 44 cases tested
- 2/3 recent hospitalized, 2 HCW and possible 4 died
- 26/47 were new cases (55 %)
- 85 % belonged to spoligotype superfamilies KZN and some of the rest to Beijing

Gandhi NR, et al. Lancet 2006; 368:1575-80

Outcome of MDR/XDR TB in Korea 1996-2005

	XDR	MDR	P Value
HIV	0/43	0/168	
Bilateral, cavity findings (%)	46.5	29.8	0.042
Cure and complete	53.5	64.9	
Relapse rate (%)	4.7	2.4	
Adjunctive surgery (%)	55.8	23.2	< 0.01

CID 2007; 45:1290-5.

INH or rifampicin was added in 33/43 cases

Outcome of MDR/XDR TB in Peru

	XDR	MDR	P Value
HIV	0/48	9/587	1.00
Bilateral, cavity findings (%)	57.8	55.0	0.72
No. of days to culture conversion	90	61	0.008
Cure and complete	60.4	66.3	0.36
Relapse rate (%)	6.9	3.8	
Adjunctive surgery (%)	14.6	14.4	

NEJM 2008; 359:563-74.

Cycloserine, co-amoxiclav, clofazimine, PAS, moxifloxacin

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SLD Susceptibilities of Thai MDR-TB 99 Isolates (2001-2002)

Drugs	% Susceptible
Amikacin / Kanamycin	95
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Para-aminosalicylic acid	85
Ethionamide	78
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XDR-TB was found in 2 %, all were sensitive to ethionamide and PAS

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Patients with XDR-TB
Siriraj Hospital, 2003-2005

- Among 28 patients with MDR-TB who had SLD determination, only 2 had XDR-TB (7 %), both had HIV co-infection
- All had non-cavitary CXR, were sensitive to ethionamide, PAS, and linezolid (1 with clarithromycin, levofloxacin, and moxifloxacin)
- One had died, the other could not determine outcome
- 7 with quinolone-resistance and 1 with amikacin-resistance were identified, 1/5 with blood tests was HIV-infected

Proposed Drugs for XDR-TB in Thailand

- Ethionamide
- *P*-aminosalicylic acid
- Cycloserine
- Linezolid
- Co-amoxiclav / Clofazimine / Clarithromycin
- Levofloxacin / Moxifloxacin

Recommendations to Prevent and Control XDR-TB

- Basic strengthening of TB and HIV control
- Improvement of management of XDR-TB suspects
- Strengthened management of XDR-TB and treatment designed
- Standardization of the definition of XDR-TB
- Increase HCW infection control and protection
- Implementation of immediate XDR-TB surveillance activities
- Initiation of advocacy, communication, and social mobilization activities

Gandhi NR, et al. Lancet 2006; 368:1575-80

Isolated Isoniazid Resistant TB

- Prevalence of 0-17 % in new cases and 4-54 % in previously treated cases
- Low-level resistance (MIC > 0.2 < 1.0 µg/mL) may respond to higher than usual dose (10-20 mg/kg/d)
- Very high-level resistance (MIC > 5.0 µg/mL) is usually found in MDR-TB
- Response to Category I in ~ 80 %, relapse ~ 20 % which may turn to MDR-TB in ~ 10 %
- Early encountered, usually response to 2 SRZE/6 RE, or 6 RZE, may be augmented with fluoroquinolones
- Late encountered, switch to RZE for another 4 months or RE for the total of 9-12 months

Isolated Rifampicin Resistant TB

- Very low prevalence in new cases and low (< 2%) in previously treated cases
- Should be speculated for whether be MDR-TB
- Usually response to 2 HEZOfx/10-16 HE, may be augmented with aminoglycosides

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A 50-year-old woman, DM, smear + TB, had persistent positive smears until 5 months after SSCC, with also worsening of symptoms and CXR. Initial response to empirical MDR-TB regimen and then failure at 6 months.

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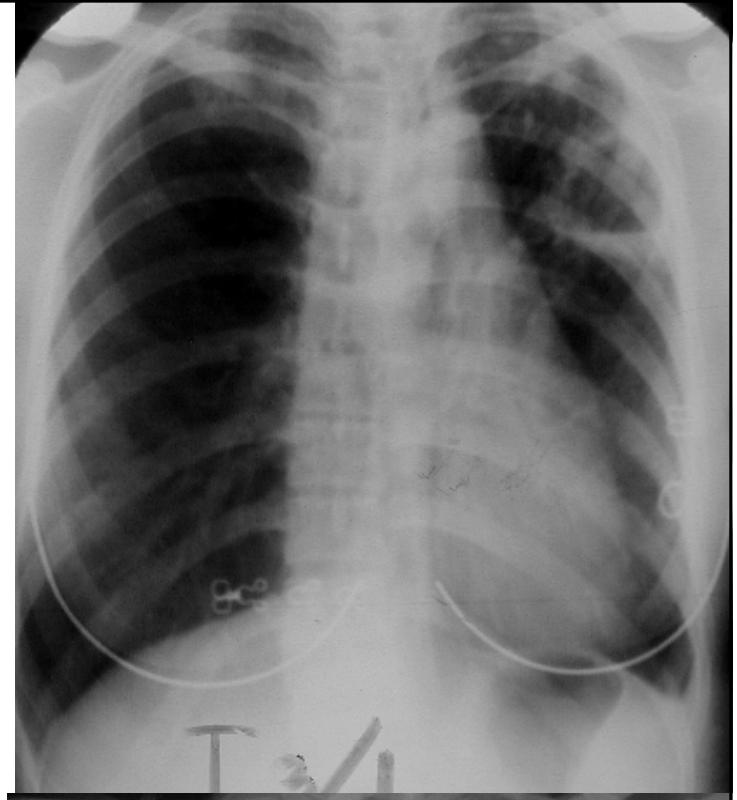

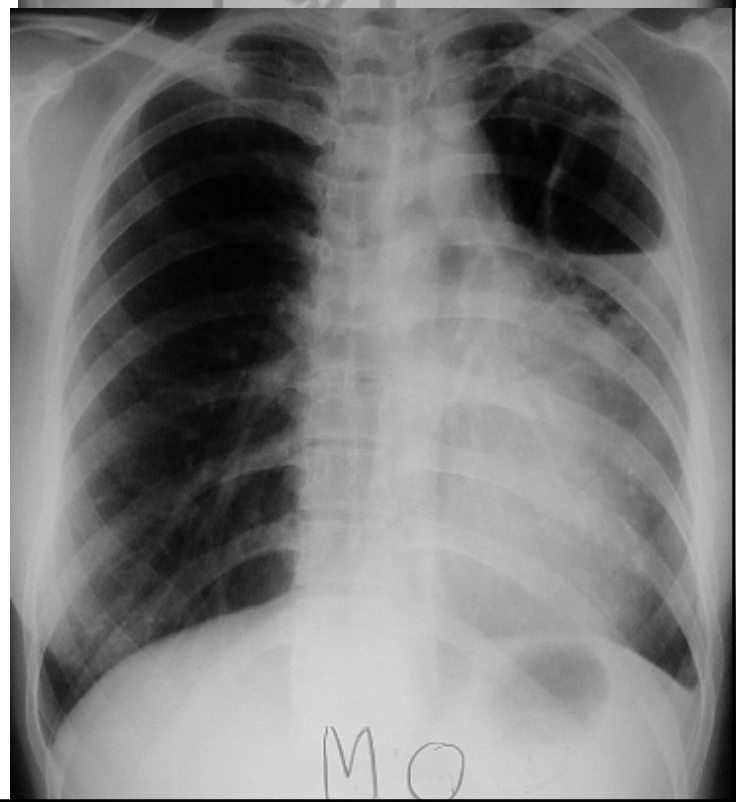

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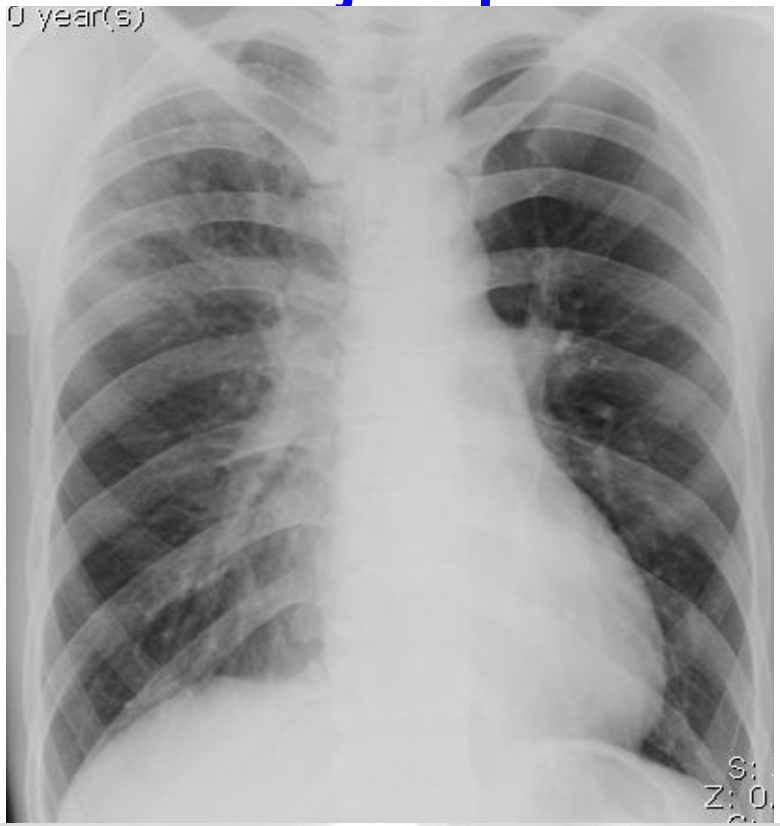
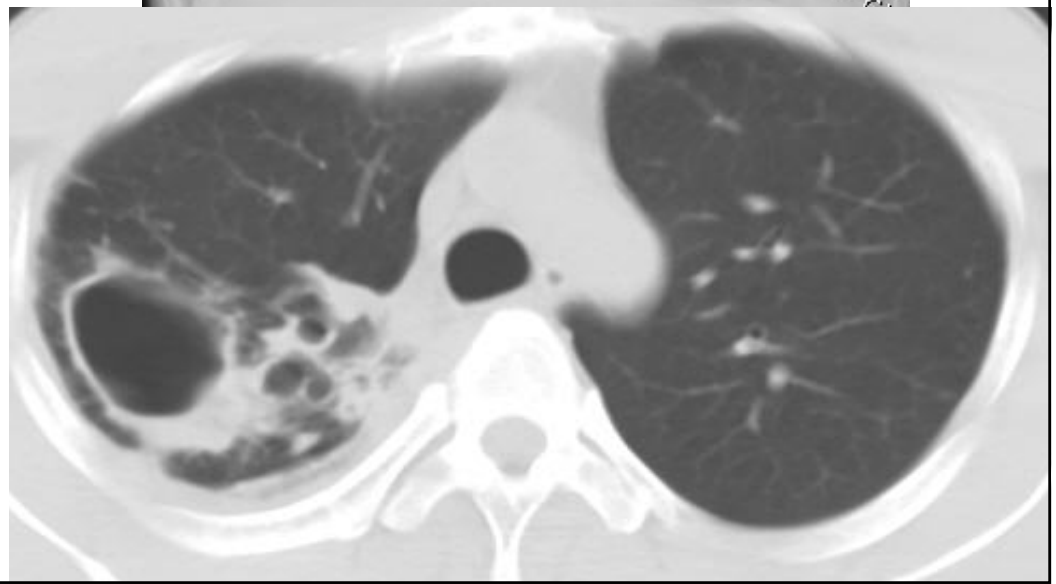
Surgical Treatment for MDR-TB : Siriraj Experience

- Cavity 3 , bronchiectasis 3, endobronchial 1
- Medical treatment failure 5, frequent relapse 1, compromised main airway 1
- DM 3, ICU nurse 1
- Lobectomy 4, segmentectomy 2, bronchial reconstruction 1
- No immediate complication, cure in 6, the other relapsed after 12 months leading to dead





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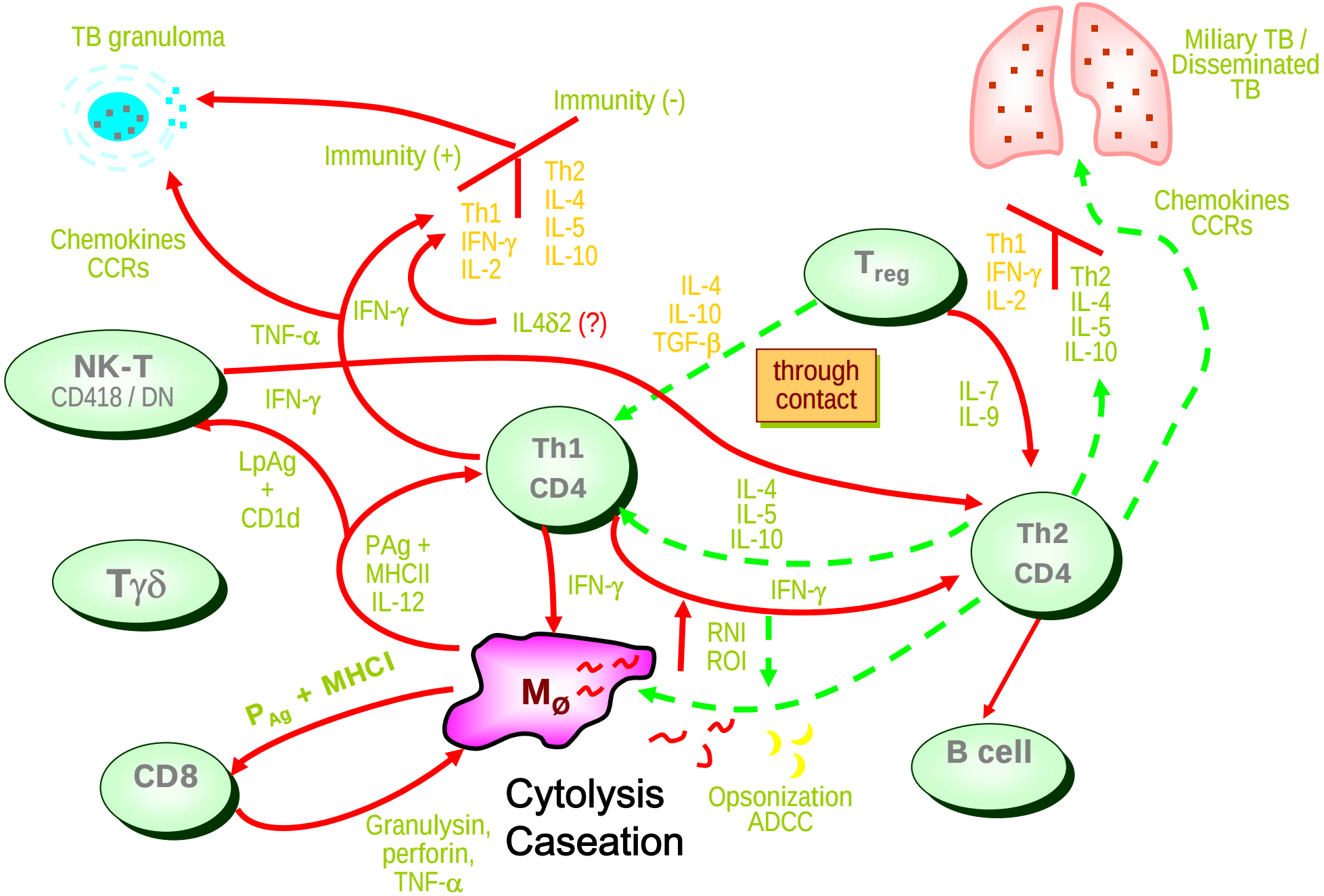
Pathogenesis of TB: Immunologic Aspects

(Adapted from Sharma SK et al Lancet Infect Dis Vol 5 July 2005)



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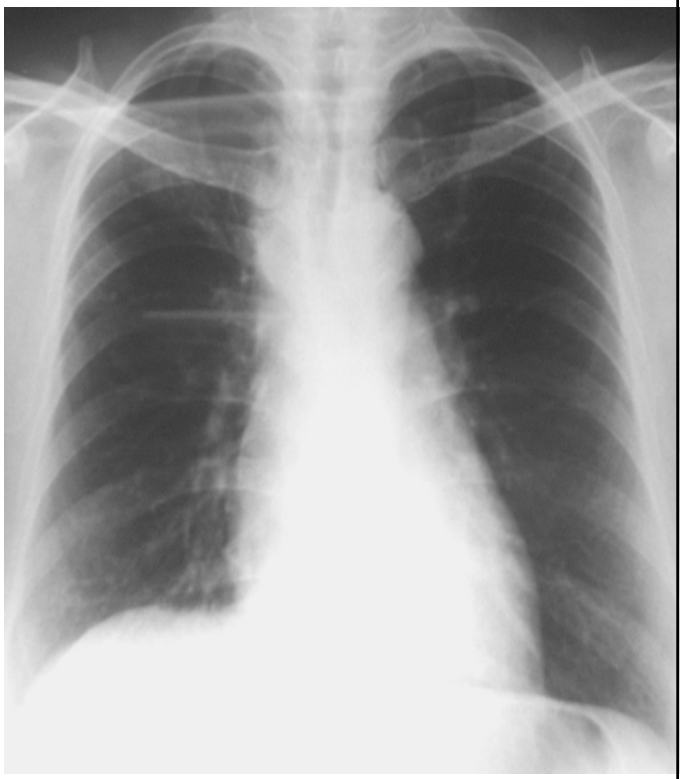

1. Disconcordance between in vitro DST and in vivo response
2. True MDR-TB
3. Specimen mislabeling
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Concerning in the Evaluation of DR-TB

- Wrong diagnosis
- Laboratory error
  - Sample mislabeling
  - Cross contamination
  - Technical assurance
- Disconcordant results
- Slow response
- Initial NTM infection or superimposed colonization
- Paradoxical response

Management of DR-TB Patients

- Secure the diagnosis
- Appropriate categorize
- Optimum initial DST
- Directly observed therapy (DOT)
- Individualize adjustment according to DST results
- Well control of co-morbid conditions
- Adjunctive surgical treatment or other modalities