



# Management of Childhood TB: Retreatment Cases

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# Content

- Background information: mechanisms of drug resistance and characteristics of childhood TB
- Retreatment cases defined
- Case scenarios
- Program for management of MDR TB



# Questions we ask

- Is this really a retreatment case?
- How can I confirm this present illness?
- Will first line drugs still work?
- Is this possibly a drug-resistant case?



# How does drug resistance develop and spread?

1. transmitted drug resistance
  - from an infected adult case – confirmed by DST, demise while on treatment, repeated treatment
  
2. acquired drug resistance
  - spontaneous mutations
  - directly proportional to the number of bacilli present:  $> 10^6$
  - caseous foci (intrathoracic lymph node disease) contain  $10^4 - 10^5$
  - pulmonary cavities (adult-type lung disease) contain  $10^7 - 10^9$



# How does drug resistance develop and spread? (cont.)

- risk is highest in patients with lung cavities and low in children with paucibacillary disease
- results from poor drug regimens
  - adding a single drug to a failing regimen
  - prescribing a weak combination of drugs
  - interruption of drug intake
  - non-adherence to treatment regimen

# Guidance for the Management of Childhood TB, WHO 2006

Table 3 Recommended treatment regimens for children in each TB diagnostic category

TB diagnostic category	TB cases	Regimen <sup>a</sup>	
		Intensive phase	Continuation phase
III	New smear-negative pulmonary TB (other than in category I).  Less severe forms of extrapulmonary TB	2HRZ <sup>b</sup>	4HR or 6HE
I	New smear-positive pulmonary TB  New smear-negative pulmonary TB with extensive parenchymal involvement  Severe forms of extrapulmonary TB (other than TB meningitis – see below)  Severe concomitant HIV disease	2HRZE	4HR or 6HE <sup>c</sup>
I	TB meningitis	2RHZS <sup>d</sup>	4RH
II	Previously treated smear-positive pulmonary TB: relapse treatment after interruption treatment failure	2HRZES/1HRZE	5HRE
IV	Chronic and MDR-TB	Specially designed standardized or individualized regimens (see treatment guidelines for MDR-TB (4) and Annex 3)	



# WHO Guidance

- Retreatment cases that are smear negative?
- Several times retreated?
- “Failure of category I treatment in children should be managed in the same way that failure in adults is managed, either with a category II or IV regimen”



# International Standard for TB Care (ISTC) Standard 11

- Patients who have failed, defaulted from, or relapsed should always be assessed for drug resistance.
- DST should be done at the start of therapy for all previously treated patients.
- Patient counseling, education and infection control measures to minimize transmission.





# Monitoring retreatment cases

- Schedule of follow up:
  - At 2 weeks; 2nd month
  - monthly
- Monitor
  - daily drug intake/compliance
  - Clinical response (weight, disappearance of signs/symptoms, drug reactions)
  - Sputum microscopy, culture (month 3, 5, and end of treatment)



# Retreatment case of TB

- Previously treated case or a patient who has received anti-TB drugs for more than a month:
  - Relapse
  - Failure
  - Return after default
  - Non-adherence



# Relapse

- Patient previously treated for TB and was declared cured or treatment completed
- Recurrence of signs and symptoms
- Requires ascertaining compliance to previous treatment and not a case of unrecognized treatment failure



# Relapse

- Due to a quiescent or persistent bacterial population which did not proliferate during initial treatment
- Absence of conditions necessary for selecting spontaneously resistant mutant bacilli present
- Cases of relapse may be re-infection
  
- Management:
  - Culture and DST
  - Drug regimen for smear positive:  
2HRZES/1HRZE/5HRE
  - For other cases: re-start same regimen
  - Supervise treatment



# Treatment Failure

- Patient who remains smear positive after 2\* months or becomes smear positive while on treatment **OR**
- Patient whose TB symptoms persist or are worsening with continued weight loss

\*WHO Treatment Guidelines for TB, 2010 and Desk-guide for diagnosis and management of TB in children 2010 IUATLD



# Treatment Failure

- Most children with TB will start to show signs of improvement after 2 to 4 weeks of anti-TB treatment
- Treatment failure suggests the possibility of MDR TB and needs careful assessment.



# Treatment Failure

- Due to a population of bacilli that is metabolically active and proliferates during treatment
- Favorable conditions for selection of naturally resistant mutant bacilli present
- Implies resistance to all of the drugs being administered at the time when failure was diagnosed
- Management:
  - Culture and DST are imperative
  - Drug regimen for smear positive: 2HRZES/1HRZE/5HRE
  - Refer to a specialist or to a PMDT treatment center
  - Supervise treatment; follow-up closely



## Return After Default (RAD) (return after lost to follow-up)

- Patient who has interrupted treatment for more than two (2) months
- Has persistence or recurrence of TB symptoms, with or without weight gain.
- Positive bacteriology (smear or culture) may or may not be present





# Return After Default

- Patients who abandon all of their drugs
  - do not incur an elevated risk of selection of resistance, since the drugs were effective when the patient took the treatment
  - the entire bacillary population resumes growth, as before the initial treatment.
- Management:
  - Culture and DST
  - Drug regimen for smear positive:  
2HRZES/1HRZE/5HRE
  - For other cases: re-start original regimen
  - Supervise closely



# Non-adherence to treatment

- Erratic intake of anti-TB drugs
- patients who omit one of the drugs generate conditions for the selection of microorganisms spontaneously resistant to the drugs the patient continues taking.
- When this condition recurs over a period of weeks or months, there could be selection of resistant bacilli
- Poor adherence is a common cause of “treatment failure”



# Non-adherence to treatment

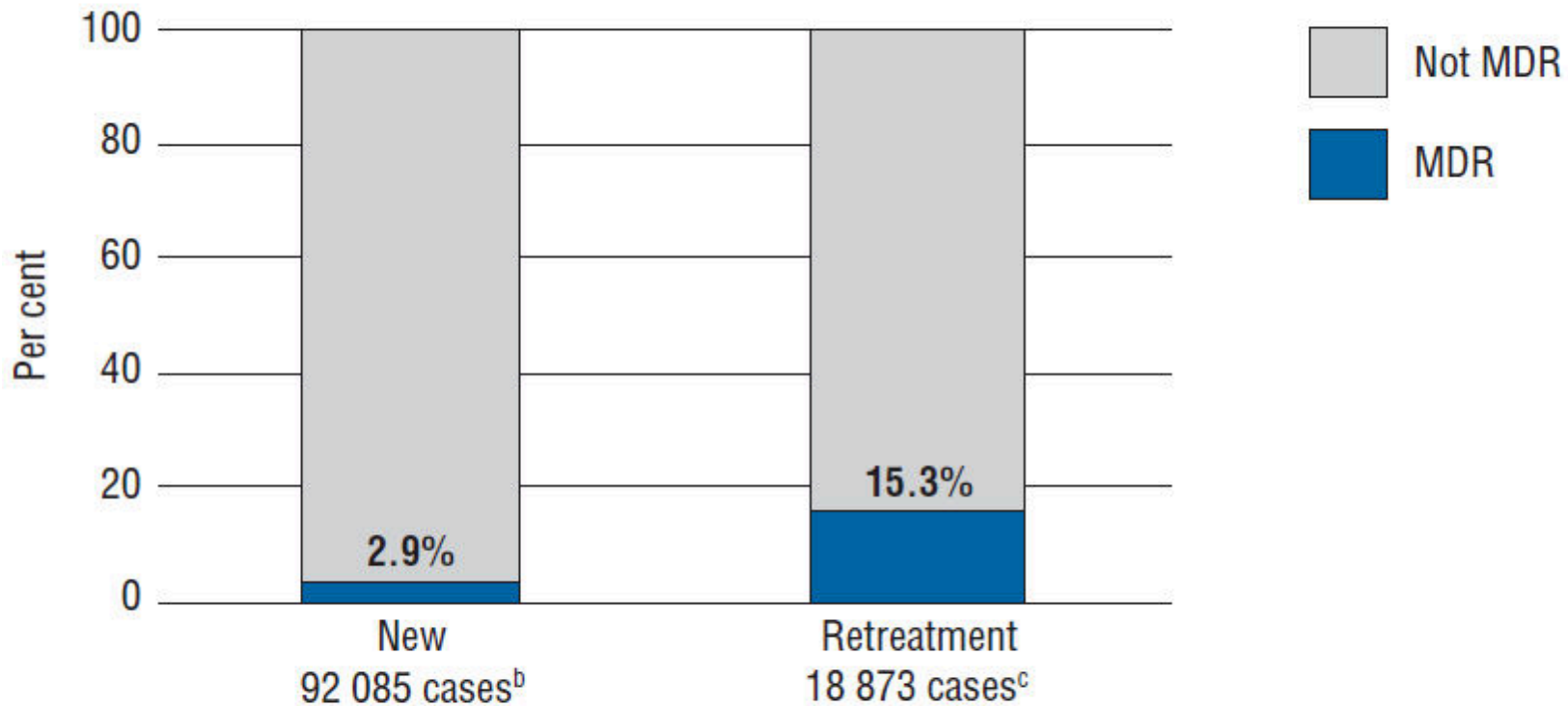
- **Management:**
  - Culture and DST
  - Drug regimen for smear positive:  
2HRZES/1HRZE/5HRE
  - For other cases: resume previous regimen
  - Supervise treatment



## Two basic conditions to reduce the number of retreatment cases

- Following of standardized initial treatment regimens
- Strict monitoring of drug intake

Figure 3.1 WEIGHTED MEAN OF MDR-TB IN NEW AND RETREATMENT TB CASES FROM DRUG RESISTANCE SURVEYS, 1994–2007<sup>a</sup>

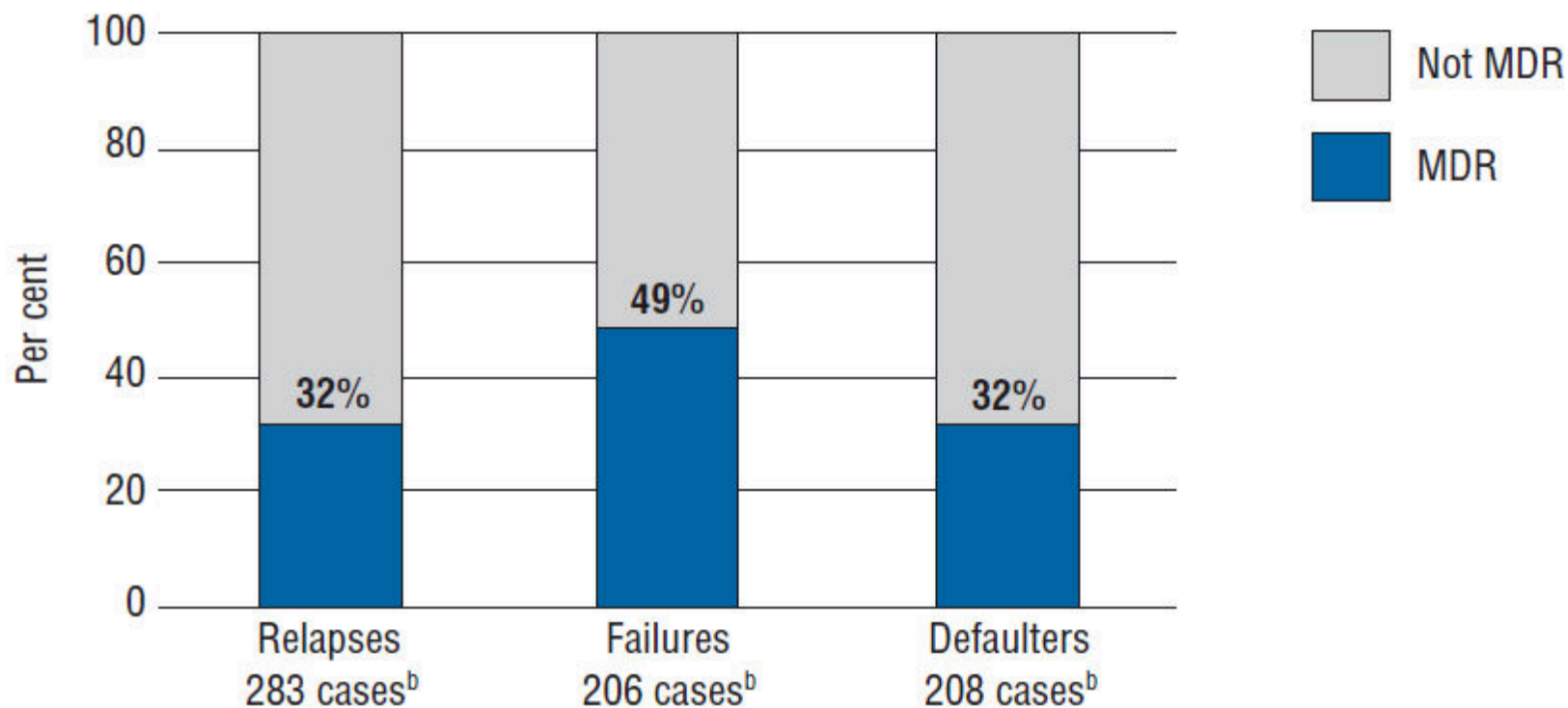


<sup>a</sup> Source: *Anti-tuberculosis drug resistance in the world: fourth global report*. Geneva, World Health Organization (2008) (8).

<sup>b</sup> Data from 105 countries or 127 settings.

<sup>c</sup> Data from 94 countries or 109 settings.

Figure 3.2 MDR IN RETREATMENT TB CASES FROM DRUG RESISTANCE SURVEYS AND SURVEILLANCE IN 10 COUNTRIES, 1997–2007<sup>a</sup>



<sup>a</sup> Source: van Gemert W et al. *MDR among sub-categories of previously treated TB cases: an analysis in 12 settings*. Presented at: 40th World Conference on Lung Health, 3–7 December 2009, Cancun, Mexico.

<sup>b</sup> Data from 12 settings in 10 countries.

# Philippine drug-resistance survey

Patient Classification	2004	2012*
	MDR	MDR
New	4%	2%
Retreatment	21%	20%

\*Partial data from the National Tuberculosis Reference Laboratory, RITM, DOH



# Case scenario (I)

- 2 years after completing a 6 month course for TB disease, Edwin, now a 7 yr old boy was brought to your clinic because of poor appetite, weight loss, prolonged fever, associated with cough. CXR showed minimal infiltrates and perihilar adenopathies. Smear was negative for AFB.
- Assessment?





# Case scenario (I)

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- Assessment: Relapse
- Treatment Regimen?



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- Assessment: Relapse
- Treatment Regimen: 2HRZ/4HR
- What else should you do?



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- Assessment: Relapse
- Treatment Regimen: 2HRZ/4HR
- What else should you do?
  - Collect sputum for culture and DST
  - Look for source case
  - Education
  - supervised treatment



## Case scenario (2)

- Jenny, 10 y/o, started treatment for TB 2 months ago at a clinic in the province and now is brought to you because of recurrence of cough, poor appetite and weight loss. On history the mother explained that Jenny has not been taking her medicines regularly because of financial constraints to buy the medicines. Jenny has been taking her medicines on and off. Smear is positive for AFB.
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## Case scenario (2)

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- Assessment: Non-adherence to treatment regimen
- Treatment regimen?



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- Assessment: Non-adherence to treatment regimen
- Treatment regimen?
  - Start 2HRZES/1HRZE/5HRE with close supervision or DOT
- What else should you do?



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- Assessment: Non-adherence to treatment regimen
- Treatment regimen?
  - Start 2HRZES/1HRZE/5HRE with close supervision or DOT
- What else should you do?
  - Collect sputum for culture and DST
  - Explain to the mother and child the importance of adherence and completing treatment



## Case scenario (3)

- Kim is 8 yrs old and was diagnosed to have TB disease based on symptomatology and CXR findings of hilar adenopathies and right lobar infiltrates, and a positive TST. Treatment with anti-TB drugs was started. At the end of 2 months, he still has cough and has not gained weight. CXR shows slight increase in infiltrates and AFB smear done showed 3+ result.
- Assessment?





## Case scenario (3)

- Kim is 8 yrs old and was diagnosed to have TB disease based on symptomatology and CXR findings of hilar adenopathies and right lobar infiltrates, and a positive TST. Treatment with anti-TB drugs was started. At the end of 5 months, he still has cough and has not gained weight. CXR shows slight increase in infiltrates and AFB smear done showed 3+ result.
- Assessment: Treatment Failure
- Treatment regimen?



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- Assessment: Treatment Failure
- Treatment regimen? 2HRZES/1HRZE/5HRE



## Case scenario (3)

- After 2 months on the regimen Kim has minimal improvement and though his weight is no longer decreasing he has not gained weight. On deeper interview of the mother you learn that the patient's 60 year-old grandmother who lived with them for several years died from TB while on treatment.
- The result of TB culture shows a growth of *M. tuberculosis*. DST result is not yet available.
- Assessment?



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- Assessment: Failed treatment 2x and probable MDR TB
- Plan?

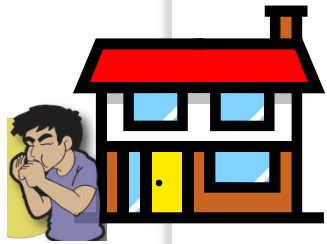


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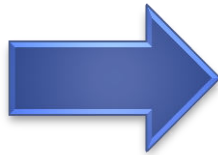
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- The result of TB culture shows a growth of *M. tuberculosis*. DST result is not yet available.
- Assessment: Failed treatment 2x and probable DR TB
- Plan: Refer to a specialist or to a PMDT treatment center

# Programmatic Management of Drug-resistant TB (PMDT)

- Govt. DOTS facilities
- Pvt. facilities/ referring health providers
- Hospitals



Identification and referral of suspects

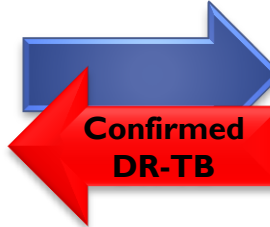


TC or STC



Category IV treatment

Screening, assessment, sputum collection



Confirmed DR-TB

Quality Assured Laboratory



DSSM, TB Culture, DST





# Conclusions

- Retreatment TB which includes relapse, failure, default, non-adherence may not require change in drug regimen.
- True failures have the highest risk for MDR TB and severely ill patients should be referred for MDR TB management
- Retreatment cases that are smear negative and have paucibacillary disease often can be treated with the same regimen.
- All effort should be exerted to send specimens for TB culture and DST
- Management of retreatment cases should be closely supervised

**The End**