Recognizing MDR-TB in Children

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Objectives

- Review the definitions and categorization of drug-resistant tuberculosis
- Understand the emergence of drug resistance
- Know the global and local MDR TB situation
- Learn how to recognize and diagnose MDR TB

Definitions

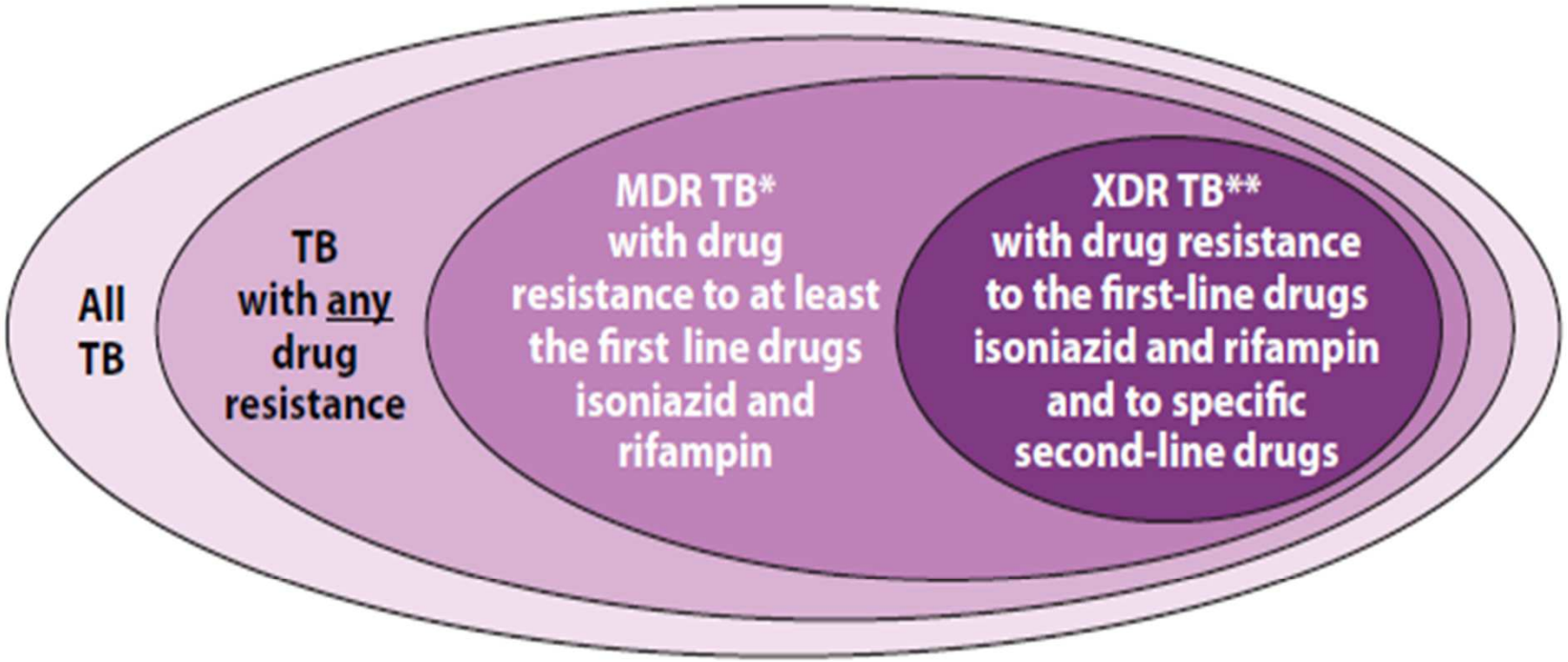
MDR TB: TB isolate that is resistant to both isoniazid and rifampin

XDR TB: MDR + resistance to fluoroquinolone and 1 of the 3 injectable drugs (amikacin, kanamycin, capreomycin)

Definitions

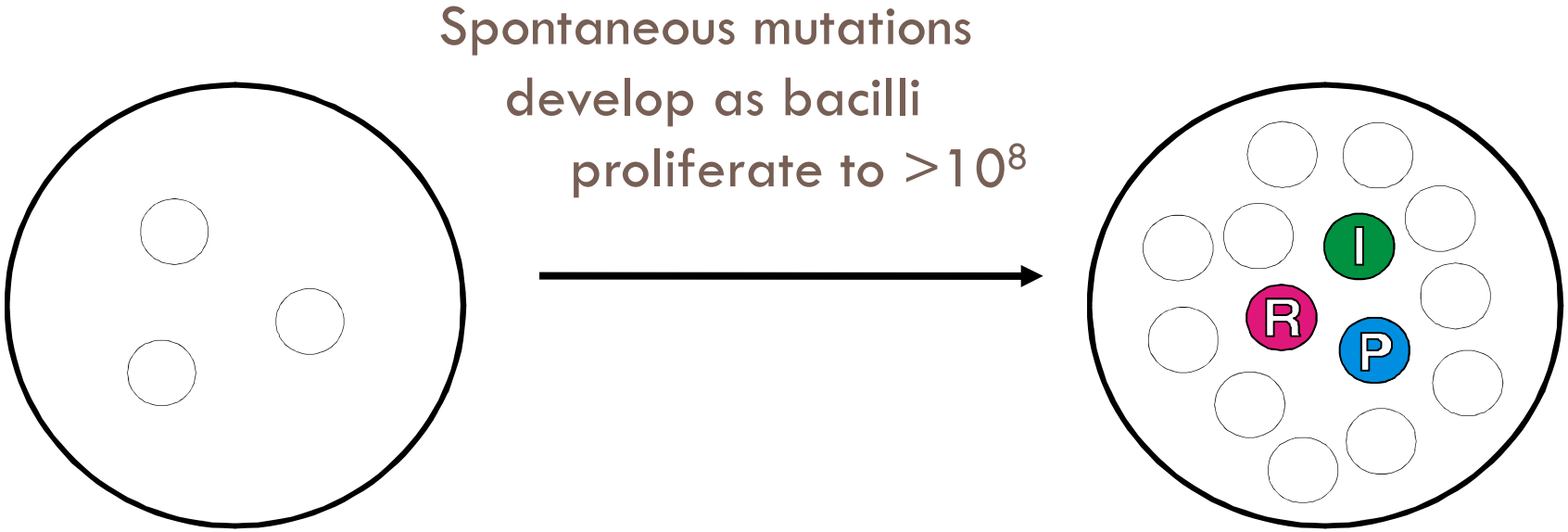
- **Primary drug resistance:**
  - Infected with TB which is already drug resistant
  - New case
- **Secondary (acquired) drug resistance:**
  - Drug resistance develops during treatment
  - Retreatment case – relapse, lost to follow up, treatment failure

The Universe of TB



* Often resistant to additional drugs

** Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)

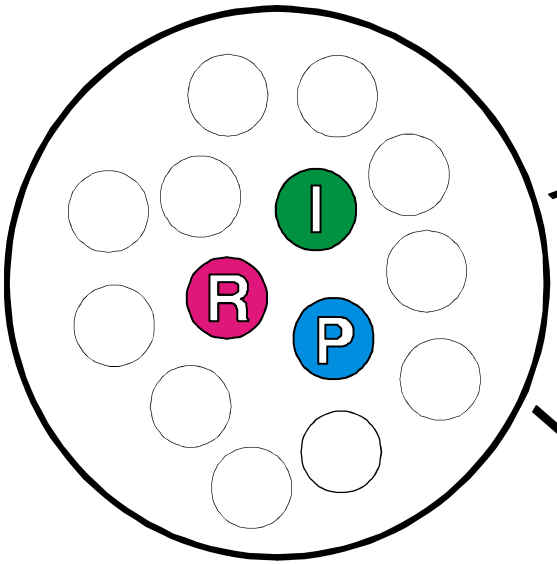


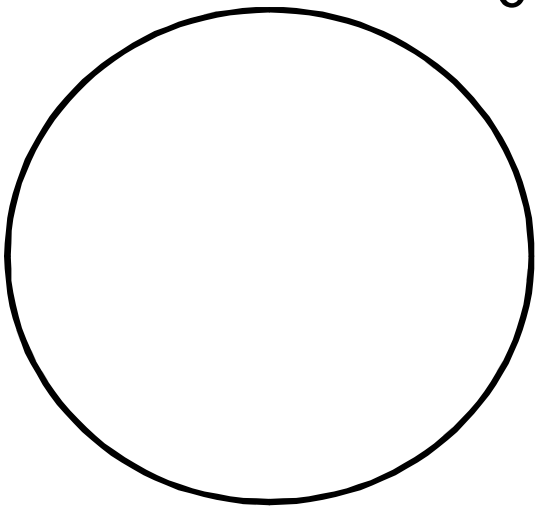
Drug	Mutation Rate
Rifampin	**10^{-8}**
Isoniazid	**10^{-6}**
Pyrazinamide	**10^{-6}**

Drug-resistant mutants in large bacterial population

Multidrug therapy:
No bacteria resistant to all 3 drugs

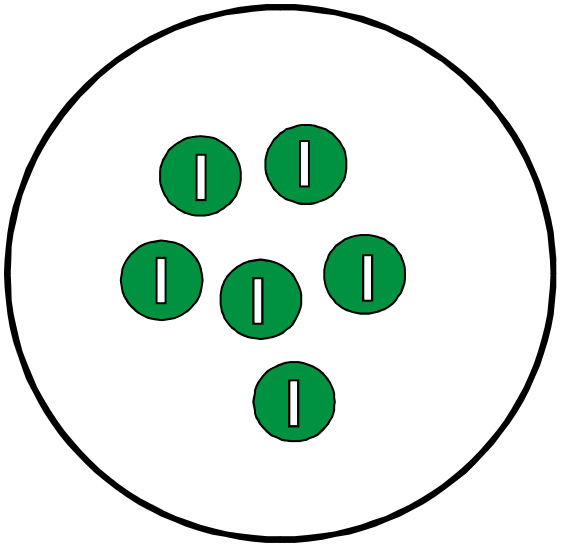
INH
RIF
PZA

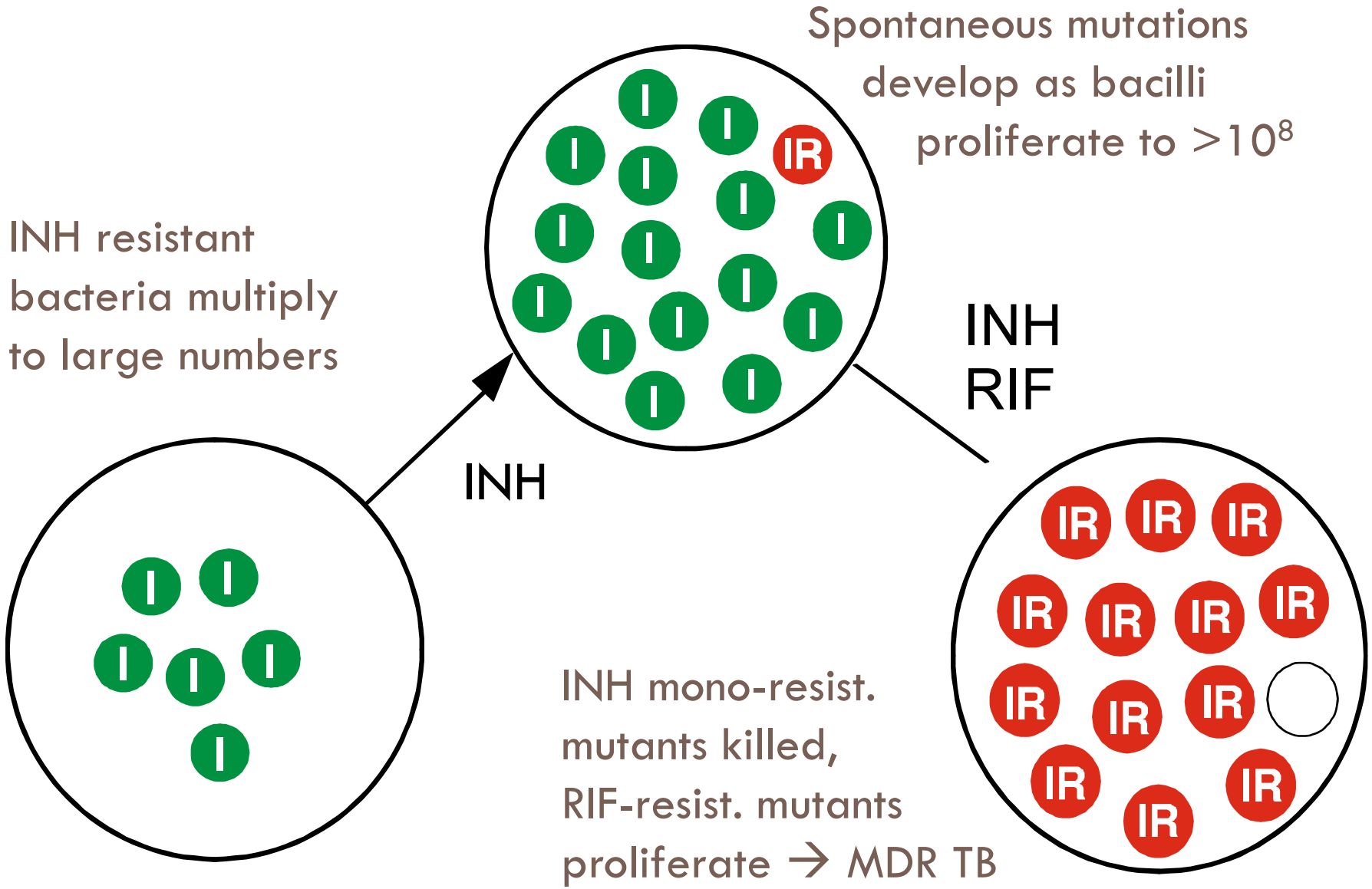




Monotherapy: INH-resistant bacteria proliferate

INH




Spontaneous mutations
develop as bacilli
proliferate to >10^8
INH resistant
bacteria multiply
to large numbers
INH
INH
RIF
IR
INH mono-resist.
mutants killed,
RIF-resist. mutants
proliferate → MDR TB

DR TB can occur when drugs are misused or mismanaged

- Patients do not complete the full course of treatment
- Health care providers prescribe the wrong treatment, the wrong dose, or wrong length of time for taking the drugs
- Drug supply is not always available
- Drugs are of poor quality

Drug-Resistance Among TB Cases

- About 3.6% of new tuberculosis (TB) patients in the world have multidrug-resistant strains.
- Levels are much higher – about 20% - in those previously treated for TB.
- About 10% of MDR-TB cases are also resistant to the two most important second-line drug classes, or XDR-TB.

High risk of infection in children who are contacts of MDR-TB patients

- In 119 South African children less than 5 years of age who had contact with an adult with MDR-TB in the prior 30 months:
  - 12% had active TB
  - 51% had latent infection (TST+)
  - 37% had no evidence of infection

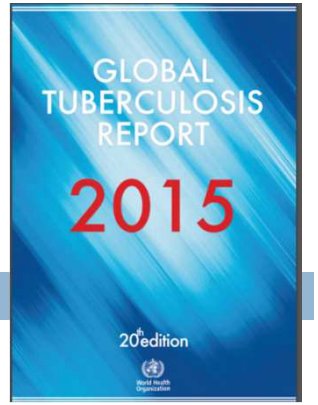
Schaaf HS, Gie RP, Kennedy M, et al. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. *Pediatrics* 2002;109(5):765-71.

Household contacts of MDR-TB patients almost always have MDR-TB

- A Peru study looked at 4503 household contacts of 693 MDR-TB and XDR-TB index patients:
  - 117 (2.6%) had active TB at the time the index patient began MDR-TB treatment;
  - 242 contacts developed TB during 4-year follow-up;
  - Of the 359 cases of active TB, 142 had DST, of whom 129 (91%) had MDR-TB.

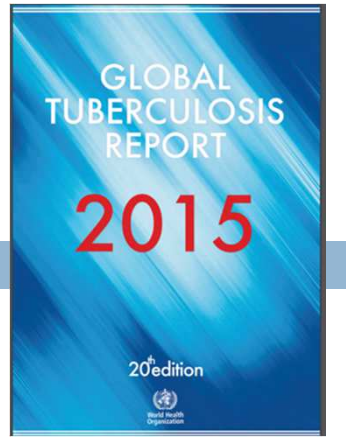
Becerra MC, Appleton SC, Franke MF, et al. Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study. *Lancet* 2011; 377: 147-52.

Global TB situation in 2014



- 9.6 million people fell ill with TB and 1.5 million died from the disease.
- An estimated 1 million children became ill with TB and 140 000 children died of TB.
- An estimated 480 000 people developed multidrug-resistant TB (MDR-TB).
- The TB death rate dropped 47% between 1990 and 2015.

TB situation in children



- In 2014, 359 000 new and relapse cases among children were reported, an increase of about 30% compared with 2013.
- The largest increases were in India (about 30 000) and the Philippines (about 10 000).

MDR TB in the Philippines
National Drug Resistance Survey Data

- 2004 DRS
  - 4% among new cases
  - 21% among re-treatment cases
- 2012 DRS
  - 2% among new cases
  - 21% among re-treatment cases

National DR TB Prevalence Data

(DOH-NTP: Dr. Celine Garfin and Ms. Donna Gaviola)

	2011	2012	2013	2014	2015	Grand Total
0-4	2			3	3	8
5-9	3	2	3	3	8	19
10-14	7	5	12	10	19	53
15-24	290	241	244	316	475	1566
25-34	497	479	414	619	797	2806
35-44	584	491	444	647	943	3109
45-54	597	450	447	649	954	3097
55-64	352	280	241	363	626	1862
>=65	125	76	67	125	219	612
Grand Total	2457	2024	1872	2735	4044	13132

National DR TB Prevalence Data

(DOH-NTP: Dr. Celine Garfin and Ms. Donna Gaviola)

	2011	2012	2013	2014	2015	Grand Total
Bacteriologically-confirmed RR-/ MDR-TB	**6**	**6**	**12**	**12**	**21**	**57**
CURED	2	4	9	1		16
TREATMENT COMPLETED		1	1			2
DIED	2		1	1	1	5
LOST TO FF-UP	2	1		2	2	7
ON TREATMENT			1	8	18	27
Clinically-diagnosed MDR-TB	**5**	**1**	**1**	**3**	**7**	**17**
TREATMENT COMPLETED	3		1			4
DIED	1			1	2	4
LOST TO FF-UP	1	1			1	3
ON TREATMENT				2	4	6
Other DR-TB	**1**		**2**	**1**	**2**	**6**
CURED			1			1
TREATMENT COMPLETED	1			1		2
DIED			1			1
ON TREATMENT					2	2
Grand Total	**12**	**7**	**15**	**16**	**30**	**80**

Approach to diagnose MDR TB in children

- Careful history

  History of contact with MDR TB case is critical information
  Consider in child failing first-line TB treatment despite adherence

- Clinical examination
- Investigations relevant for suspected PTB or EPTB

  Important to try to get samples for culture and DST

- HIV testing

  Failure to respond to TB treatment should consider HIV-related lung disease that is not TB as well as the possibility of MDR TB

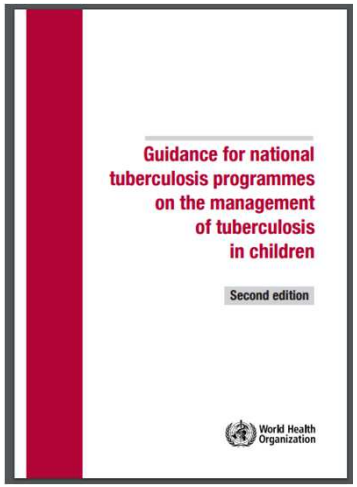
- Bacteriological confirmation and drug susceptibility testing whenever possible

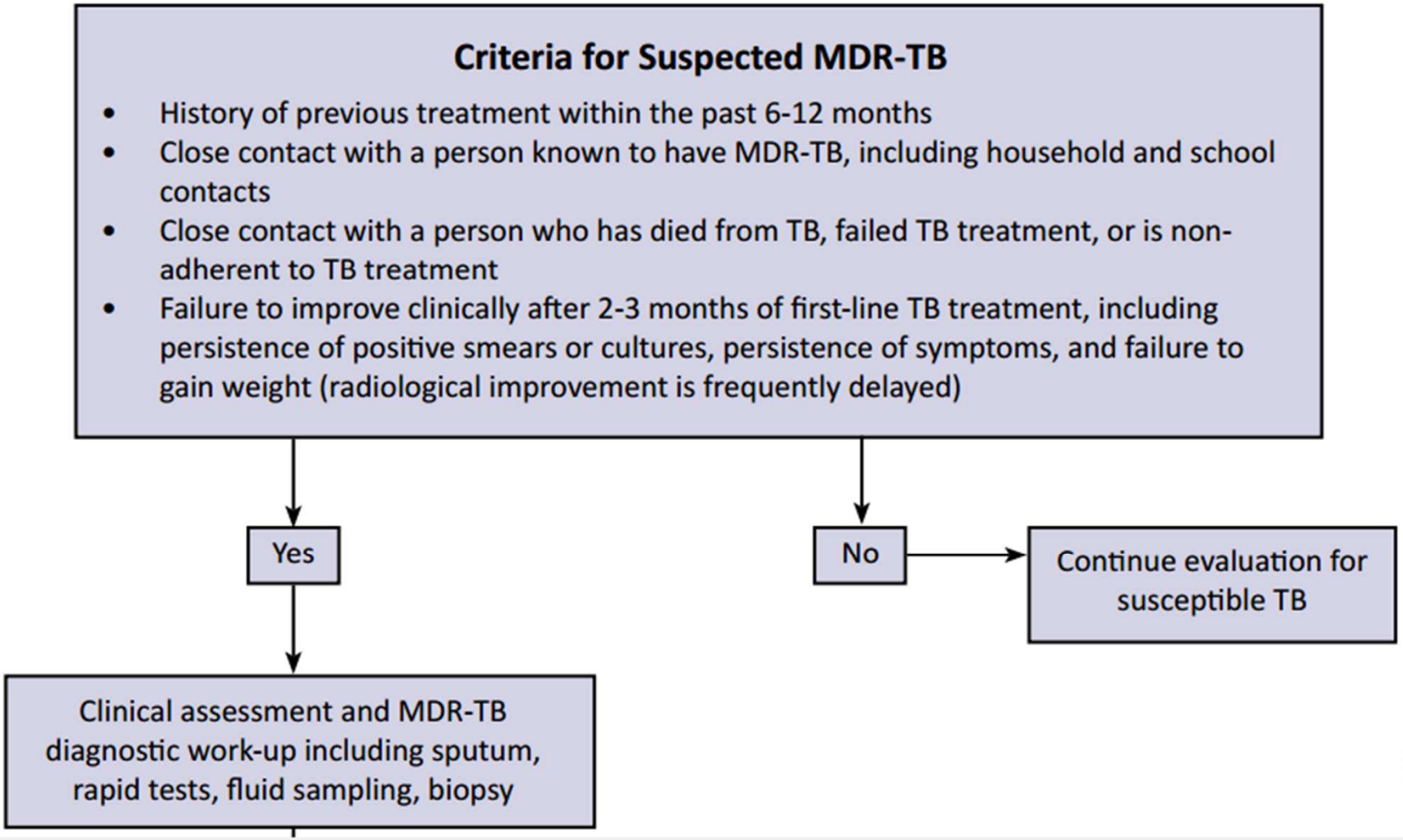
  Sputum (or other relevant samples e.g. lymph node aspiration) should be collected in all children with suspected MDR TB for culture with drug sensitivity testing (or LPA or Xpert MTB/RIF)

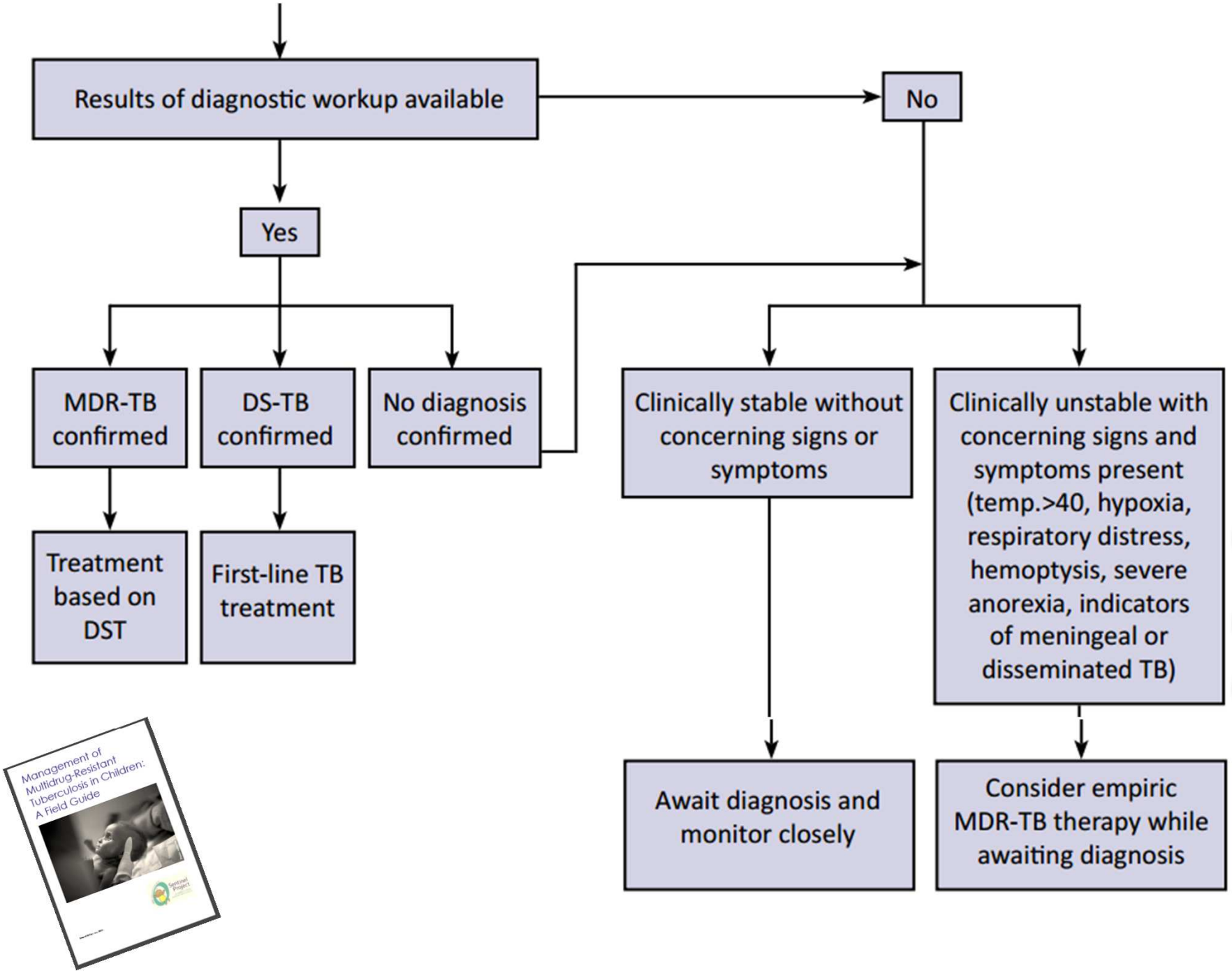
Drug-resistant TB should be suspected when:

- there is contact with known DR-TB;
- there is contact with suspected DR-TB, i.e. source case is a treatment failure or a retreatment case or recently died from TB; -
- a child with TB is not responding to first-line therapy despite adherence;
- a child previously treated for TB presents with recurrence of disease.

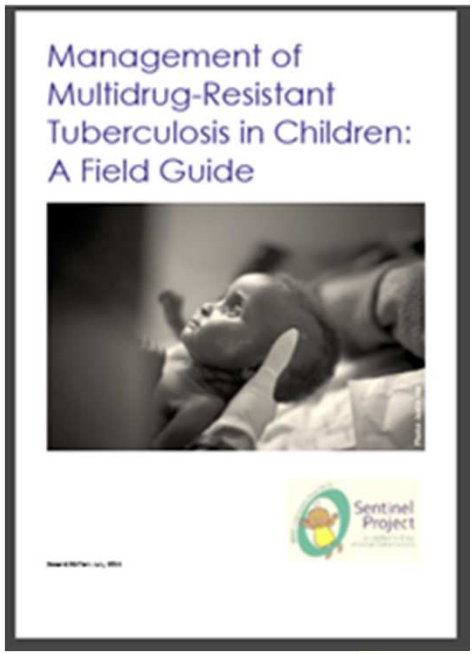
- When DR-TB is suspected, every effort should be made to confirm the diagnosis by obtaining specimens for culture and DST.
- Rapid DST of iNH and RIF or of RIF alone is recommended over conventional testing or no testing at the time of diagnosis.




Criteria for Suspected MDR-TB
History of previous treatment within the past 6-12 months
Close contact with a person known to have MDR-TB, including household and school contacts
Close contact with a person who has died from TB, failed TB treatment, or is non-adherent to TB treatment
Failure to improve clinically after 2-3 months of first-line TB treatment, including persistence of positive smears or cultures, persistence of symptoms, and failure to gain weight (radiological improvement is frequently delayed)
Yes
No
Continue evaluation for susceptible TB
Clinical assessment and MDR-TB diagnostic work-up including sputum, rapid tests, fluid sampling, biopsy


Results of diagnostic workup available
No
Yes
MDR-TB confirmed
DS-TB confirmed
No diagnosis confirmed
Clinically stable without concerning signs or symptoms
Clinically unstable with concerning signs and symptoms present (temp.>40, hypoxia, respiratory distress, hemoptysis, severe anorexia, indicators of meningeal or disseminated TB)
Treatment based on DST
First-line TB treatment
Await diagnosis and monitor closely
Consider empiric MDR-TB therapy while awaiting diagnosis
Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide

Case scenarios



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TB CARE II

DR TB TRAINING NETWORK

https://www.drtbnetwork.org/clinical-case-series/027-child-mdr-tb

Case scenario 1

S> A 7-year-old boy is brought to the OPD

- "lumps" in neck and "coughing all the time"
- Father died of TB last year, even though he took his medications every day

O> P.E. - Cachectic, febrile 39°C, HR 137, multiple cervical LN, cool to touch, round and rubbery

- chest retractions, minimal expansion of the right hemithorax, right side of chest is dull to percussion, and no breath sounds

A>critically ill, MDR TB considered

P> emergency thoracentesis with removal of 600 cc of straw-colored fluid; sputum sample sent for smear, culture, and rapid DST.; regimen for MDR TB started

Case scenario 1

- 2 days later: Xpert MTB/RIF test showed Rifampicin resistance to RIF (RR)
- final culture results: resistance to INH, RIF, EMB, and SM

- After 2 years: because he was started on treatment quickly, patient fully recovered and remains an active, playful 9-year-old (having completed 2 years of treatment when he was seven) at the top of his class in school.

Case scenario 2

- An 11-yo girl being treated for TB (cough, fever, weight loss, hemoptysis)
- (+) AFB smear, was started on HRZE and received DOT at a LHC, compliant
- 1st mo: smear (-), feeling "better", cough and fever resolved
- 2nd mo: recurrence of cough, night sweats, smear(-)
- 3rd mo: symptoms worsened, daily fevers, smear showed "rare AFB," (was felt to be a "contamination" when a repeat smear was negative)
- Continued on HR with good compliance

Case scenario 2

- She now presents to the OPD after having coughed "two cups" of blood. She also notes a 6 kg weight loss, daily fevers, severe cough, and shortness of breath.
- P.E
- ill-appearing, cachectic, and tachycardic, diffuse crackles and wheezes all fields.
- sputum is streaked with blood
- smear shows AFB
- A repeat history is taken, no history of contacts with other TB patients and specifically state that they have no known MDR-TB contacts or risk factors. A rapid HIV test is negative.

Case scenario 2

- deemed to be at high risk for MDR-TB, as she is failing a first-line regimen given under strict DOT.
- Her sputum is sent for culture and DST.
- Empirical MDR TB regimen is started; she is hospitalized for the first 2 weeks of therapy and then returns to the PMDT Treatment Center.
- She receives daily medications under strict DOT
- Her symptoms improve, and 2 months later, her smear is negative.
- Her DST results: resistance to INH, RIF, EMB, and SM
- Her MDR TB regimen is continued and she is monitored closely for compliance and adverse events.

Case scenario 3

- 4-year-old boy brought to the hospital clinic at the end of the 6th mo of anti-Tb treatment
- Persistent cough, shortness of breath; failure to thrive
- PMHx: His mother had past history of TB
- hospitalized 7 mos ago: 4 mos of cough, fever, anasarca
- Chest xray: left upper lobe infiltrate, bilateral hilar opacities.
- Hospital staff could not obtain a sputum sample for lab tests
- He was discharged on a 6-mo course of anti-TB regimen
- The patient did poorly over the next few months with worsening cough and failure to thrive.

Case scenario 3

- P.E. (present):
- General wasting, weight 9 kg, RR 30 bpm
- Chest diffuse bilateral crackles
- Laboratory: Renal function normal, Liver function normal, Hgb 6.0 g/dL WBC 18.8 x 109/L, HIV test test, negative
- Current diagnostics: Gastric lavage - AFB 3+ and culture grew M. tuberculosis, DST showed resistance to isoniazid, rifampin, ethambutol, and streptomycin.

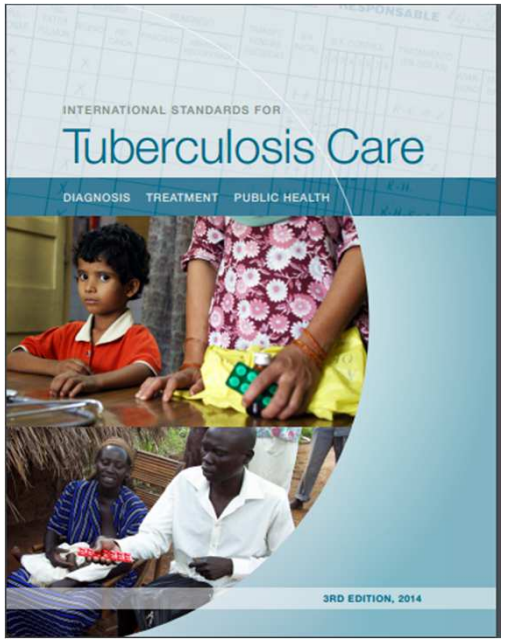
Case scenario 2

- This child received a regimen for MDR TB.
- He received nutritional upbuilding
- smear and culture converted to negative after the first month of treatment.
- After 6 months of intensive phase treatment, his weight was 11.5 kg. Chest X-ray showed improvement. His weight continued to improve. He completed treatment at 22 months. Final weight was recorded at 15.3 kg.

Take home message

- A high index of clinical suspicion is needed for timely diagnosis of MDR-TB in children.
- Risk factors include a history of previous treatment, failure to improve on first-line TB treatment, known MDR-TB contact, contact with a patient who died on TB treatment or failed TB treatment.
- Empiric treatment should be considered based on the DST of the contact or based on DST results from the child's own specimens (if available).
- Early initiation of appropriate treatment is essential to ensure good outcomes.

"All providers who undertake evaluation and treatment of patients with tuberculosis must recognize that, not only are they delivering care to an individual, they are assuming an important public health function."



Acknowledgement

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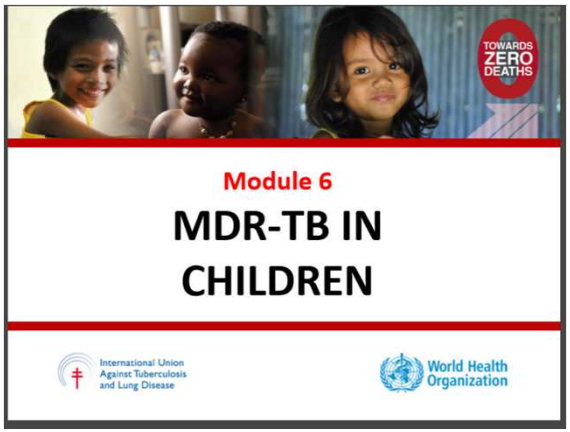
MDR-TB in Children

Session 8



Unit 11: Drug Resistance and MDR-TB

Botswana National Tuberculosis Programme
Manual Training for Medical Officers

Thank You