Module 6

MDR-TB IN CHILDREN

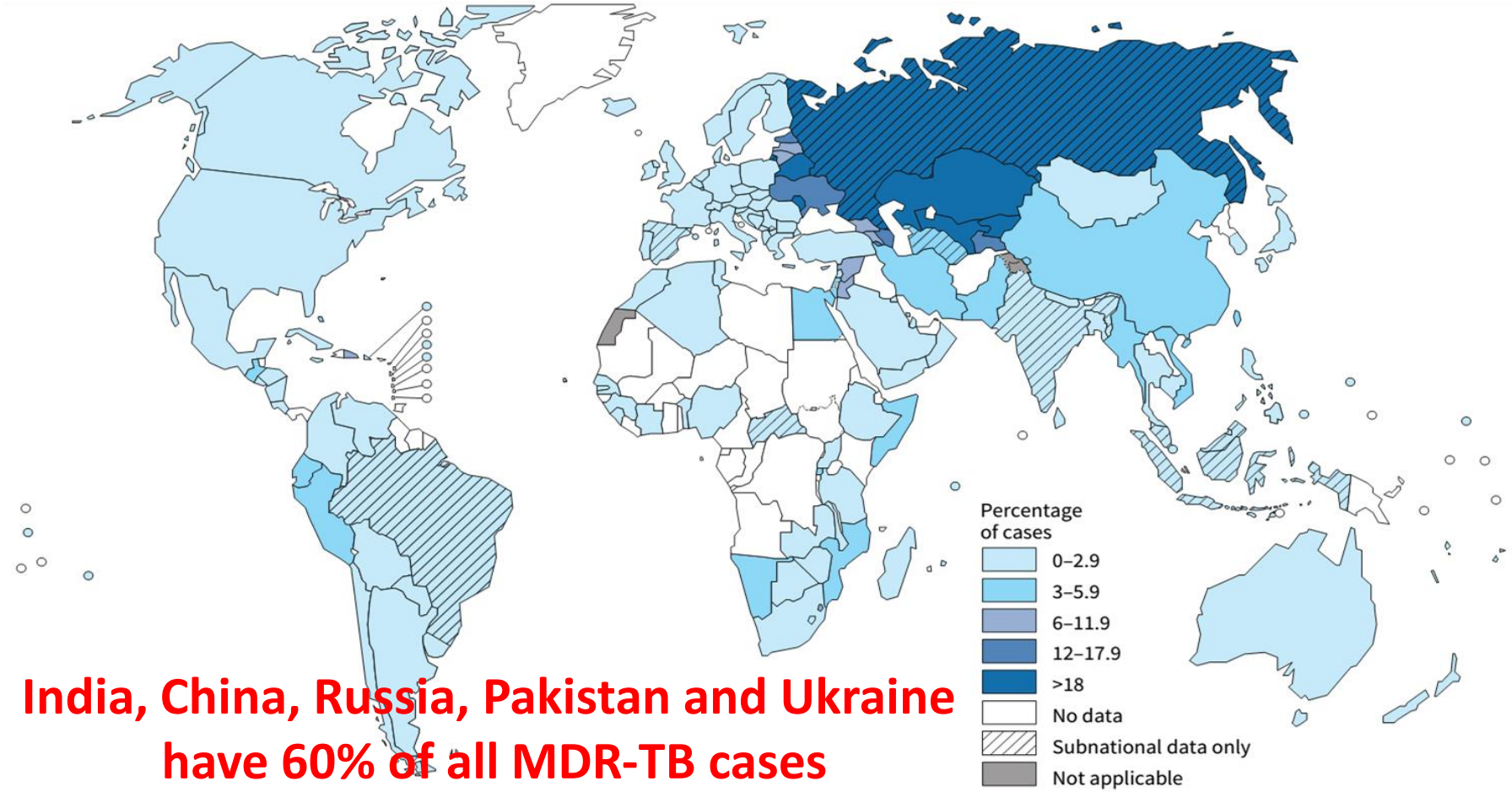
International Union Against Tuberculosis and Lung Disease

World Health Organization

MDR TB disease in children: epidemiology

- Very limited data available
- The burden of MDR TB in children is likely to reflect that which occurs in adults, so…..
- MDR TB is common in children in settings where MDR TB is common
- MDR TB is increasing in children in settings where overall MDR TB is increasing

Proportion of MDR among new TB cases
Latest available data, 2013



India, China, Russia, Pakistan and Ukraine have 60% of all MDR-TB cases

[a] Figures are based on the most recent year for which data have been reported, which varies among countries.

Insert some national MDR TB prevalence data

MDR TB disease in children: epidemiology

- MDR TB in children will mainly be from transmission of drug-resistant TB to the child, rather than acquired from prior exposure to TB treatment
- Early diagnosis and effective treatment of MDR TB cases (usually adults) is the most effective tool available to reduce transmission
- Children with MDR TB are not major contributors to the spread of MDR TB in the community
- MDR TB in children is associated with increased morbidity and mortality compared to drug-sensitive disease

Approach to diagnose TB in children

WHO Guidance 2006

1. Careful history
   - includes history of TB contact
   - symptoms suggestive of TB
2. Clinical examination
   - includes growth assessment
3. Tuberculin skin test
4. Bacteriological confirmation whenever possible
5. Investigations relevant for suspected PTB or suspected EPTB
6. HIV testing

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)

Poor response to TB treatment in HIV-infected child should consider possibility of other HIV-related lung disease as well as possibility of DR TB

Cause	Clinical features
Recurrent pneumonia	Recurrent episodes of cough, fever and fast breathing that usually respond to antibiotics
LIP	Unusual before 1 year of age Associated with generalised symmetrical lymphadenopathy, clubbing, parotid enlargement. Nutritional status variable. CXR: diffuse reticulonodular pattern and bilateral perihilar adenopathy. No compression of airways
Drug resistant tuberculosis	Persistent symptoms not responding to first-line TB treatment (usually by 2 months) despite good adherence. History of contact with known or suspected DR TB case.
Bronchiectasis	Cough productive or purulent sputum; clubbing CXR: honeycombing usually of lower lobes Complicates recurrent bacterial pneumonia, LIP or TB
PcP	Common cause of severe, fatal pneumonia especially in infants. Persistent hypoxia is common Unusual after 1 year of age CXR: diffuse interstitial infiltration or hyperinflation
Mixed infection	Common problem: LIP, bacterial pneumonia, TB Consider when poor response to first-line empiric management
Kaposi sarcoma	Uncommon Characteristic lesions on skin or palate

Practice points: diagnosis of MDR TB in a child

Confirmed DR TB is a laboratory diagnosis : culture with DST or nucleic acid amplification test (e.g. Xpert MTB/RIF)

Probable DR TB is diagnosed in a child with TB and a recent close contact with DR TB

Suspected DR TB is when a child fails to improve while adherent to first-line anti-TB treatment OR if the adult source case is a treatment failure, a retreatment case or recently died from TB

Diagnosis and management of MDR TB in a child

Children with suspected MDR TB should ideally be **referred** to a facility that can do culture and drug susceptibility testing - usually a tertiary facility

Hospitalisation is usually required for treatment because it includes injectables

Follow-up and **management of adverse events** should ideally be managed by experienced paediatrician at tertiary level

Practice points: management of MDR TB

All children with suspected MDR TB should be referred

Never add a single drug to a failing regimen

Treat according to DST results from child or from likely source case (if results from child not available)

Give at least 3 drugs, preferably 4, to which patient or adult source case is susceptible

All treatment daily and under direct observation

Caregivers need counselling and support regarding adverse effects, treatment duration and adherence

Careful monitoring for clinical response and adverse events

Approach to treatment of MDR TB in children

1. Choice of treatment will be influenced by availability of DST in child or contact, and drug resistance surveillance in a particular setting
2. Minimum of 4 active drugs if extensive pulmonary or disseminated disease
3. Start with first-line drugs to which DST results show susceptibility (e.g. ethambutol, PZA)
4. Add an injectable (e.g. amikacin)
5. Add fluoroquinolone (e.g. levofloxacin or moxifloxacin)
6. Duration 18 months – limited evidence
7. Hospitalisation for 4-6 months for injectable
8. DOT by health worker

Drugs used for treatment of MDR TB in children

Drug Group	Drug name	Daily dosage in mg/kg	Maximum dose (mg)
[a] Group 1: Oral first-line drugs	Ethambutol	20-25	2000
	Pyrazinamide	30-40	2000
[b]Group 2: Injectable agents.	Streptomycin (1st-line)	15-20	1000
Aminoglycosides	Amikacin	15-20	1000
	Kanamycin	15-20	1000
Cyclic polypeptide	Capreomycin	15-20	1000
[b]Group 3: Fluoroquinolones	Ofloxacin	15-20	800
	Levofloxacin	7.5-10	750
	Moxifloxacin	7.5-10	400
[c]Group 4: Second-line oral drugs	Ethionamide (or prothionamide)	15-20	1000
	Cycloserine (or terizidone)	10-20	1000
	[e]Para-aminosalisylic acid (PAS; 4gr sachets)	150	12g
[d]Group 5: Drugs of uncertain value	High-dose INH	15-20	400
	[f]Linezolid	10-12 twice daily	300 once/twice daily
	Amoxicillin/clavulanate	15 amoxicillin 3 x daily	
	Clarithromycin	7.5-15 twice daily	500 twice daily
	[g]Thioacetazone	3-4	150
	Imipenem/cilastatin	(only IV)	
	Clofazimine	3-5	300

a. DST could be unreliable – use as additional drug if DST result susceptible or not done[25]
b. Choose one drug in each of these groups; amikacin preferred to kanamycin in children
c. Choose one or more of these drugs to make up total of 4 new drugs
d. Consider use of these drugs if insufficient drugs to build an acceptable regimen with previous groups. Each drug only considered as half a drug, therefore 2 drugs in this group counts as one additional drug.
e. PAS is administered in acidic base (e.g. yoghurt or orange juice) for improved absorption
f. Linezolid dosage for TB is uncertain, but lower doses (300 mg twice daily or even 300 mg daily in adults) cause less adverse effects and still seem effective.[33]
g. Thioacetazone should NOT be used in HIV-infected patients

Adapt a table depending on availability of drugs in your setting

Schaaf HS, et al. Paediatr Resp Rev 2011

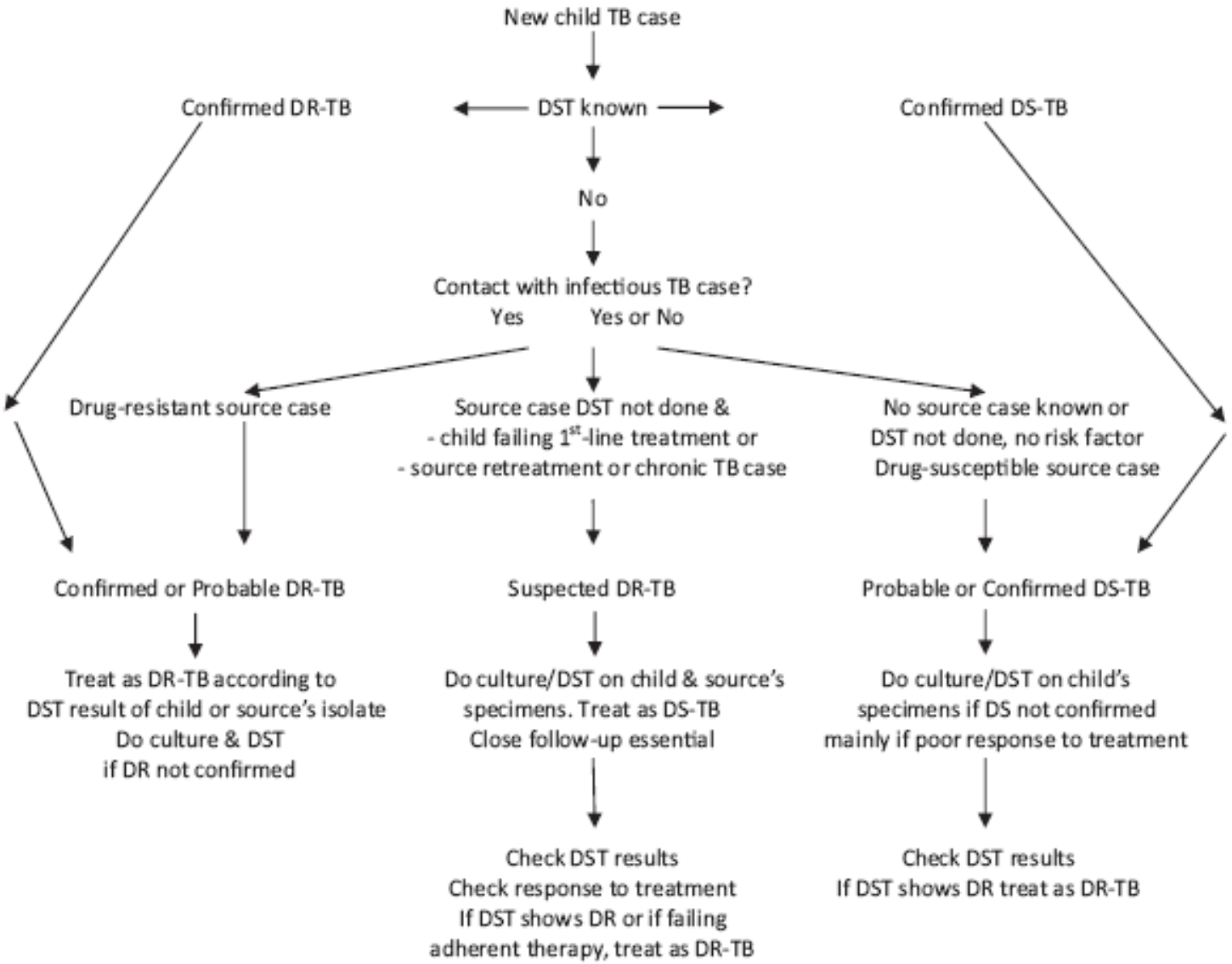
Adverse effects of drugs used for treatment of MDR and XDR TB in children

Drug	Adverse effects	How to monitor
Isoniazid	Hepatotoxicity	Jaundice, liver enzymes
	Rash	Clinical observation for
	Peripheral neuropathy (rare)	other adverse effects
	Psychosis	
Pyrazinamide	Hepatotoxicity	Jaundice, liver enzymes
	Arthralgia	Clinical observation for
	Rash	other adverse effects
Ethambutol	Optic neuritis (rare)	Vision screening if possible
Second-line injectable drugs	Ototoxicity (starts with high frequency hearing loss and may continue after stopping culprit drug)	Hearing test (audiology)
Amikacin Kanamycin	Nephrotoxicity (Renal failure and severe hypokalaemia)	
Capreomycin		Serum creatinine and potassium levels
Fluoroquinolones	Gastro-intestinal disturbance	Clinical observation and caregivers' report
Ofloxacin	Insomnia	
Levofloxacin	Arthralgia	Serum uric acid if used with pyrazinamide
Moxifloxacin		
Thioamides	Gastro-intestinal disturbance (nausea, vomiting, abdominal pain and anorexia)	Clinical observation
Ethionamide	Hepatotoxicity	Jaundice – serum alanine transferase and billirubin
Prothionamide	Hypothyroidism	Thyroid stimulating hormone and free T4 levels
Cycloserine	Psychosis, convulsions, parasthesia, depression	Clinical observation
Terizidone		
Para-aminosalisylic acid (PAS)	Gastro-intestinal disturbance (mainly diarrhoea)	Clinical observation
	Hypothyroidism	Thyroid stimulating hormone levels and free T4
Linezolid	Myelosuppression	Full blood counts
	Lactic acidosis	Serum lactate level
	Peripheral neuropathy	Clinical observation
	Pancreatitis	Clinical observation

Adapt a table depending on availability of drugs in your setting

Schaaf HS, et al. Paediatr Resp Rev 2011

Diagnostic algorithm approach to suspected or confirmed DR TB in children



Schaaf HS, et al. Paediatr Resp Rev 2011

Management of MDR TB and HIV

All children with suspected MDR TB should be tested for HIV

HIV-infected children are at high risk of severe disease and death due to DR TB

ART markedly improves outcome for MDR (and XDR) TB with no increase in adverse events - should be started early in treatment

Drug interactions are usually not a problem as regimens usually do not contain rifampicin

Patients should also receive pyridoxine and cotrimoxazole preventive therapy

Careful monitoring for clinical response and adverse events

Management of child contact of DR TB case

Identification and **symptomatic screening of all contacts** of DR TB cases is important

Symptomatic contacts require evaluation for possible TB

Investigation of symptomatic contacts should include sputum for culture and drug sensitivity (or LPA or Xpert MTB/RIF)

Asymptomatic contacts need to be followed and informed that prompt evaluation is required should symptoms develop

Management of child contact of DR TB case

There is very little evidence and **no agreed consensus** on the use of or optimal regimen for preventive therapy for asymptomatic contacts of drug resistant TB cases

One approach is not to provide any preventive therapy and opt for careful, regular follow-up informing the contact about possible symptoms of TB and that prompt evaluation is needed if symptoms develop

An alternative approach, especially for high-risk contacts such as HIV-infected or young children, is to choose a preventive therapy regimen that includes at least two drugs to which the DR TB index case is susceptible or naïve and treat for at least 6 months

Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide

USAID
FROM THE AMERICAN PEOPLE

TB CARE II

Sentinel Project

TOWARDS ZERO DEATHS

Summary

A history of contact with a suspected or proven drug resistant TB case is critical in evaluation and management of child with suspected DR TB or an asymptomatic child contact

Children with suspected DR TB should be referred if possible to specialist for investigation (culture and sensitivity), management (hospitalisation for injectables) and monitoring for toxicity to second-line drugs

HIV test is routine in evaluation of suspected DR TB and early ART improves outcome

Decisions regarding preventive therapy for at risk child contacts will be informed by drug sensitivity pattern of the index case