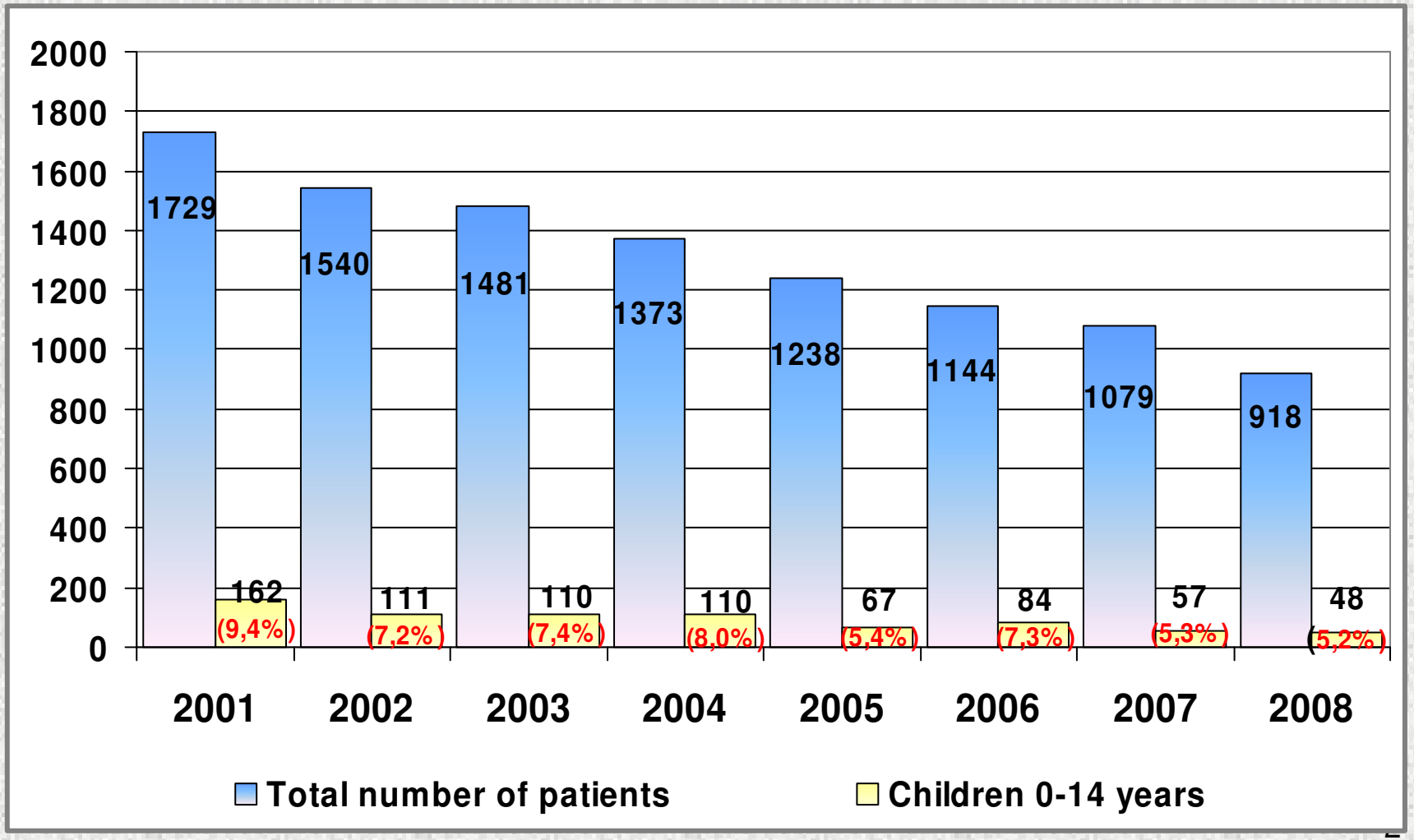
Treatment of childhood tuberculosis

Iveta Ozere

The State Agency of Tuberculosis and Lung Diseases, Latvia

IUATLD Euro Region Conference
Dubrovnik, Croatia, 27-30 May 2009

Numbers of newly diagnosed TB patients by years in Latvia

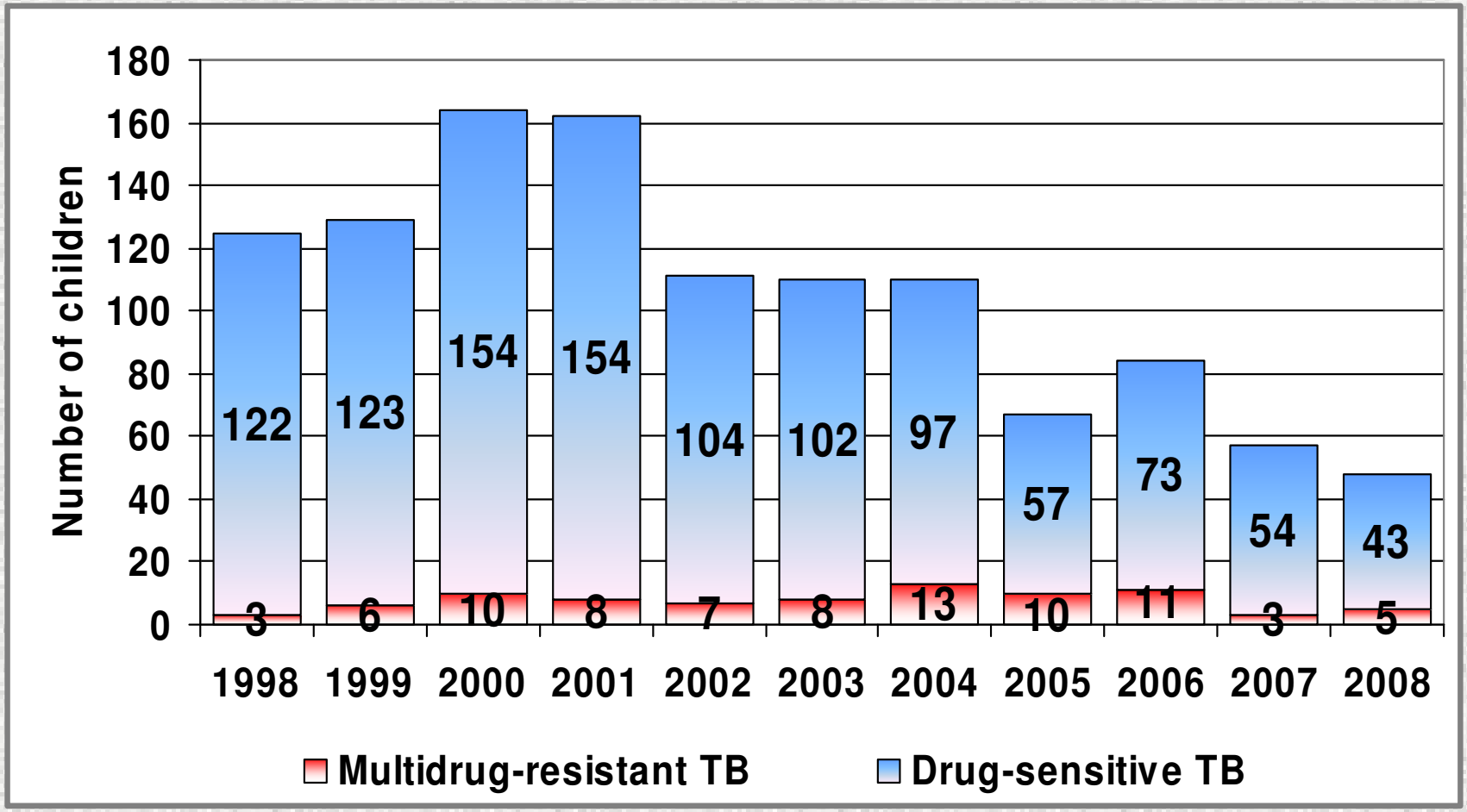


Tuberculosis in Latvia

- Despite steadily declining incidence of tuberculosis Latvia still is high MDR-TB burden country

- the proportion of primary multidrug-resistant TB in newly diagnosed patients ranged from 8,3-13,8% during 1998-2006, and the proportion of acquired MDR-TB for adults with previously treated TB reached 42,5% in 2003 gradually declining up to 24,2% in 2007

Children under 15 years of age diagnosed with drug-sensitive and multidrug-resistant TB during 1998-2008 in Latvia



Lecture outline

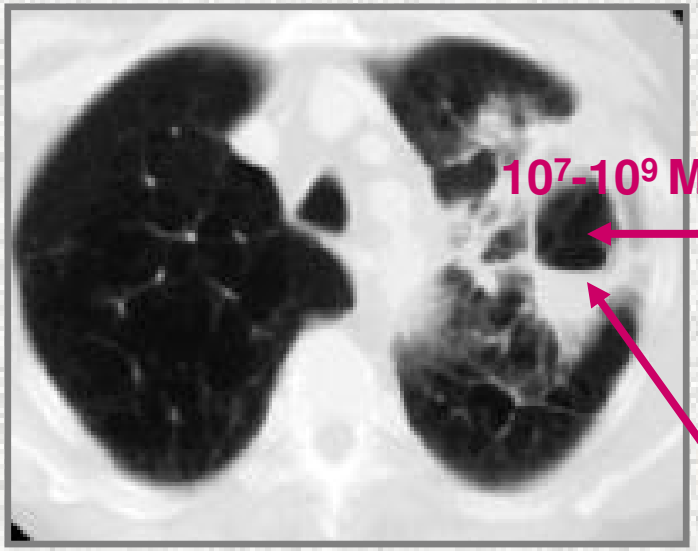
- Principles of antituberculosis therapy
- Special considerations for treatment of tuberculosis in children
- Treatment of active tuberculosis in children
- Approach to antituberculosis treatment in children in Latvia
- Clinical cases for discussion

Principles of antituberculosis therapy

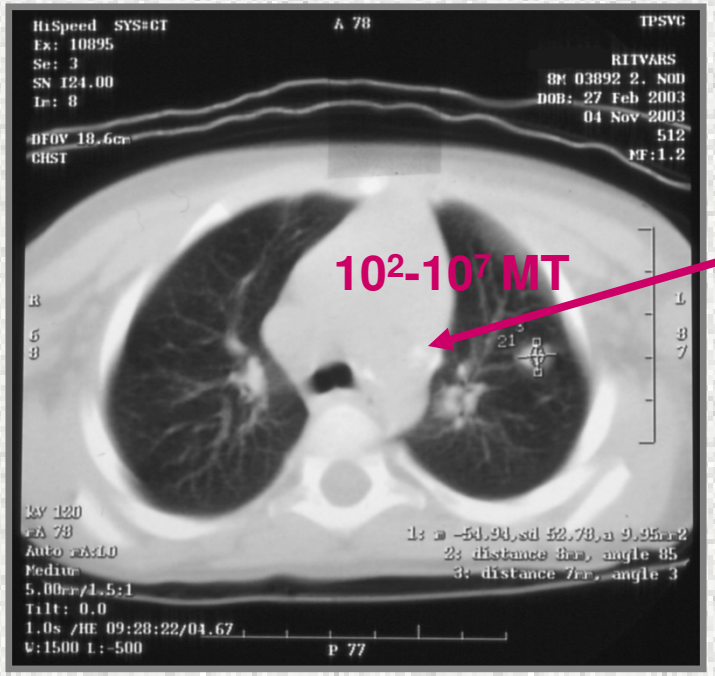
Goal of treatment- to cure the child and to prevent from relapse of the disease during life-time

To reach the goal - theoretically **eradication of all mycobacterial populations**

Mycobacterial populations residing within any tuberculosis lesion



Large numbers of actively metabolizing MT



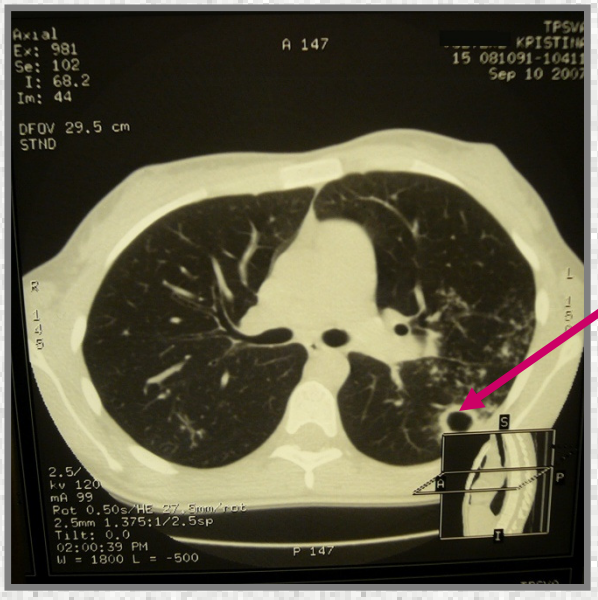
Smaller numbers of intermittently active or dormant MT

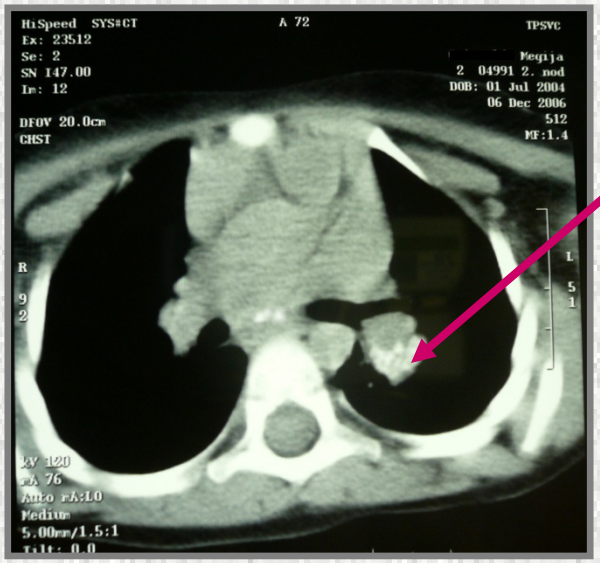
Principles of antituberculosis therapy

Activities of antituberculosis drugs

- Bactericidal
- Sterilizing
- Prevention of drug resistance to companion drugs

Activities of antituberculosis drugs





Actively metabolizing MT

Bactericidal activity

H > S > R > E > Z

Intermittently active or dormant MT

Sterilizing activity

R > Z > H > S > E

Prevention of drug resistance to companion drugs

H > R > E > S > Z

Antituberculosis drugs

Grouping	Drugs
Group 1 First line oral agents	isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z);Rifabutin (Rfb)
Group 2 Injectable agents	kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (S)
Group 3 Fluoroquinolones	moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Ofx)
Group 4 Oral bacteriostatic second-line agents	ethionamide (Eto); prothionamide (Pto); cycloserine (Cs); terizidone (Trd); p-aminosalicylic acid (PAS)
Group 5 Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv; thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high dose isoniazid (high- dose H); claritromycin (Clr)

Antituberculosis drugs

First-line oral agents

- **Isoniazid (H) –** backbone of TB chemotherapy and treatment. Bactericidal with the highest EBA
- **Rifampicin (R)** – bactericidal with high EBA and a key sterilizing drug in short-course treatment regimens of TB
- **Pyrazinamide (Z)** – high sterilizing activity. Kill slow growing tubercle bacilli in acidic pH inside macrophages
- **Ethambutol (E)** – bacteriostatic at low doses (15 mg/kg/day), bactericidal at higher doses 25 mg/kg/day. The primary role is to prevent the emergence of drug resistance to companion drugs

Treatment of tuberculosis in children – special considerations

Drug doses for children

- Studies of ethambutol, pyrazinamide and isoniazid have found lower plasma drug levels in children than adults, using the same dosages
- Young children have greater extra-vascular fluid volume and greater liver mass proportionally to body mass
- Malnourished children have higher rates of hepatotoxicity
- Children with more advanced forms of disease may experience more significant hepatotoxic reactions than less severe children

Recommended doses of first-line anti-TB drugs for adults and children

[WHO (2006) Guidance for national tuberculosis programmes on the management of tuberculosis in children]

Drug	Recommended dose			
	Daily		Three times weekly	
	Dose and range (mg/kg body weight	Maximum (mg)	Dose and range (mg/kg body weight)	Daily Maximum (mg)
Izoniazid	5 (4-6)	300	10 (8-12)	-
Rifampicin	10 (8-12)	600	10 (8-12)	600
Pyrazinamide	25 (20-30)	-	35 (30-40)	-
Ethambutol	children 20 (15-25) adults 15 (15-20)	-	30 (25-35)	-
Streptomycin	15 (12-18)	-	15 (12-18)	-

Treatment of tuberculosis in children – special considerations

Drug doses for children

WHO has revised the dosing of antituberculosis drugs in children

Drug	Daily dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid	10 (10-15)	300
*Rifampicin	15 (10-20)	600
Pyrazinamide	35 (30-40)	2000

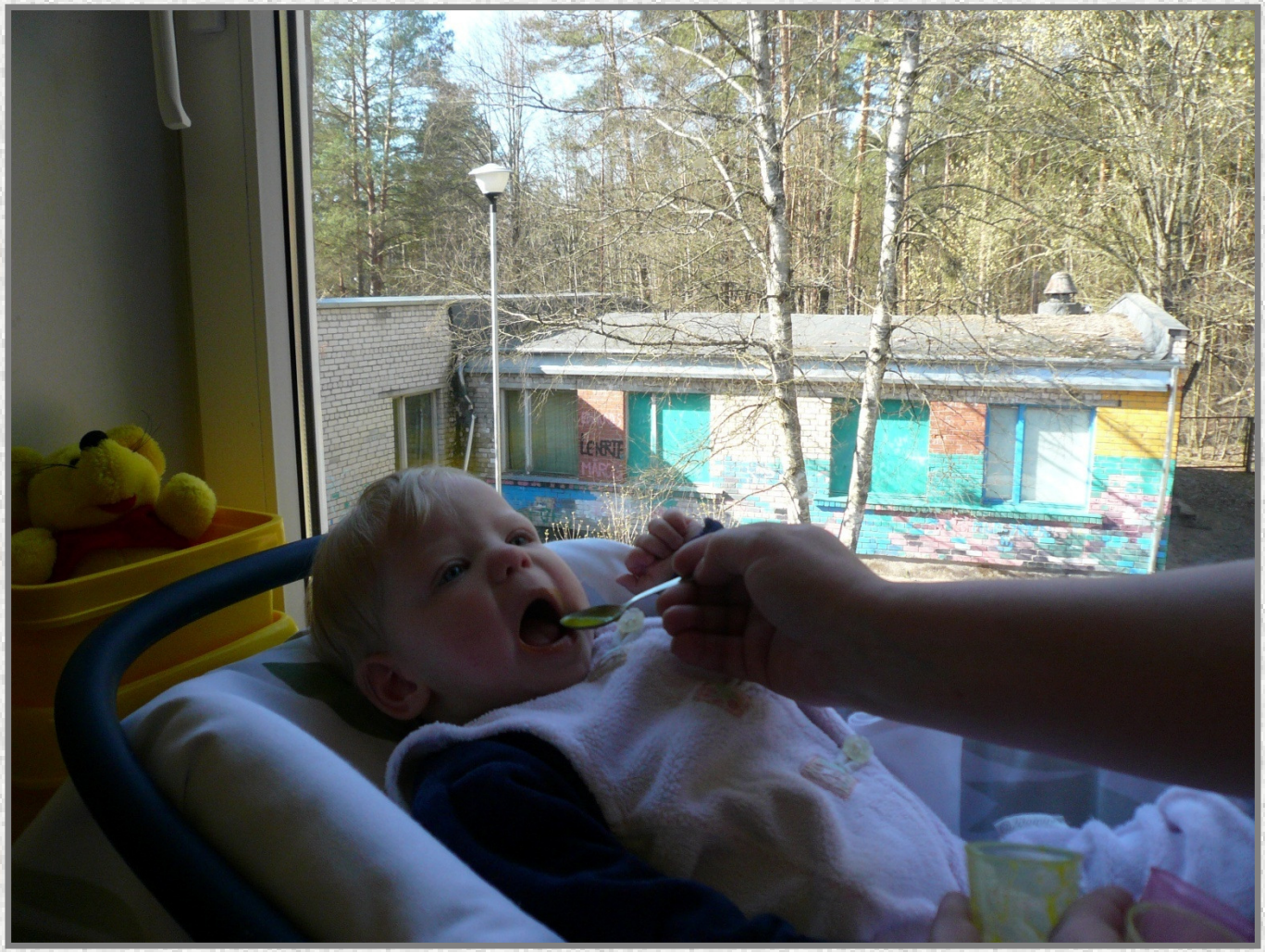
* Dosages at higher ranges may be preferable for children under 10 kg, children with HIV infection and malnutrition

Treatment of tuberculosis in children – special considerations

Drug formulations

Crushing pills and making suspensions are not well-studied and standardized

Treatment of tuberculosis in children – special considerations

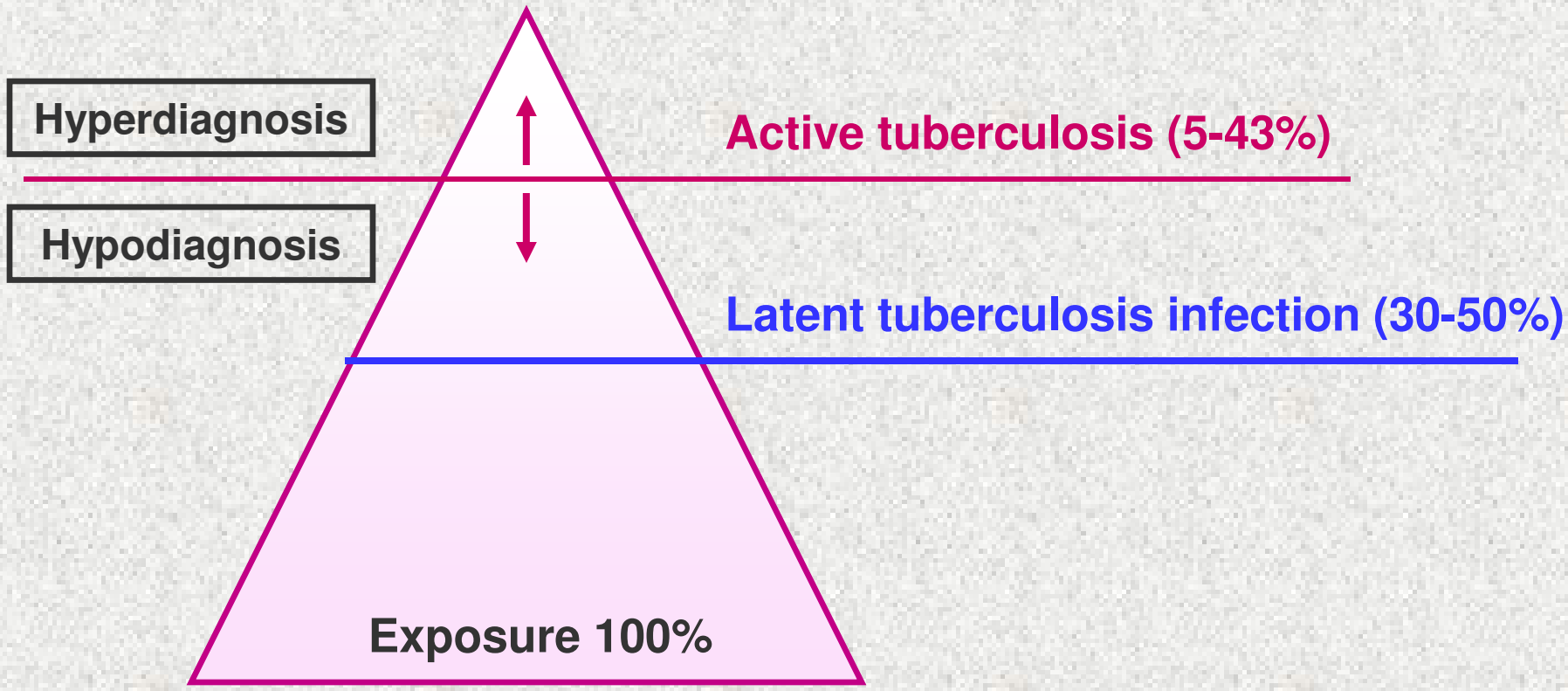


Treatment of tuberculosis in children – special considerations

Treatment of tuberculosis in children – special considerations

Stages of primary tuberculosis

In children the process of the infection flows almost imperceptibly into disease

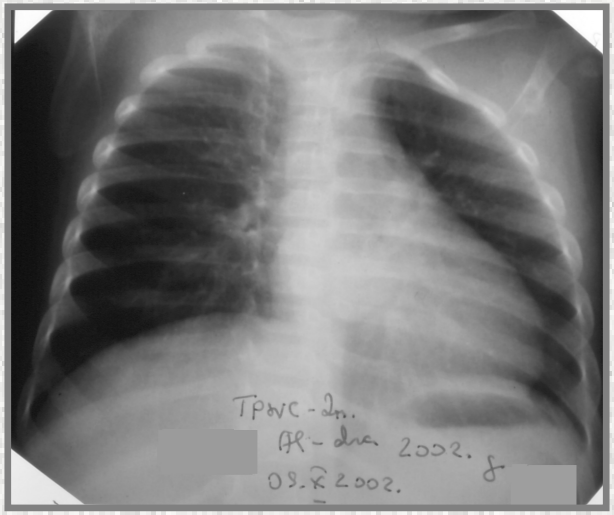


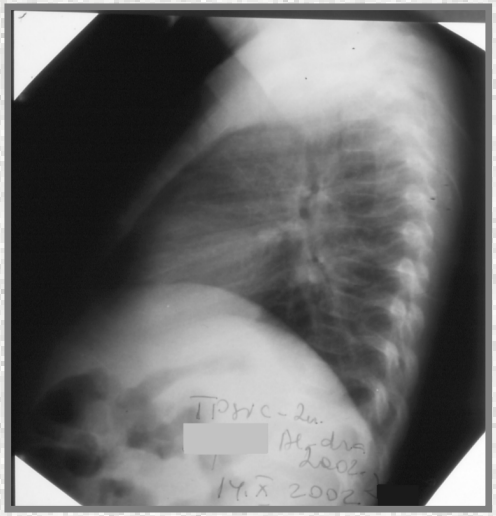
Characteristic features of childhood TB

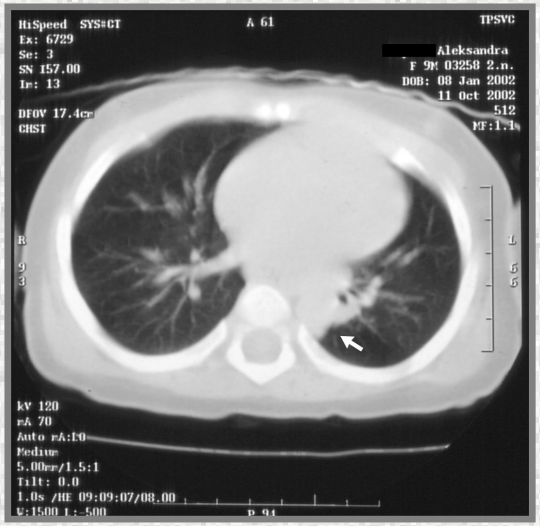
- children up to 10 years of age usually have primary tuberculosis with either inthrathoracic adenopathy alone or its combination with limited lung parenchymal involvement
- close caseous lesions contain relatively small numbers of mycobacteria, thus the significant numbers of drug resistant mutant organisms may not be present
- bacteriological confirmation is available < 50% cases depending on the extension of the disease
- most of children with TB in developed countries are discovered early through contact investigation

Typical scenario of case finding in Latvia

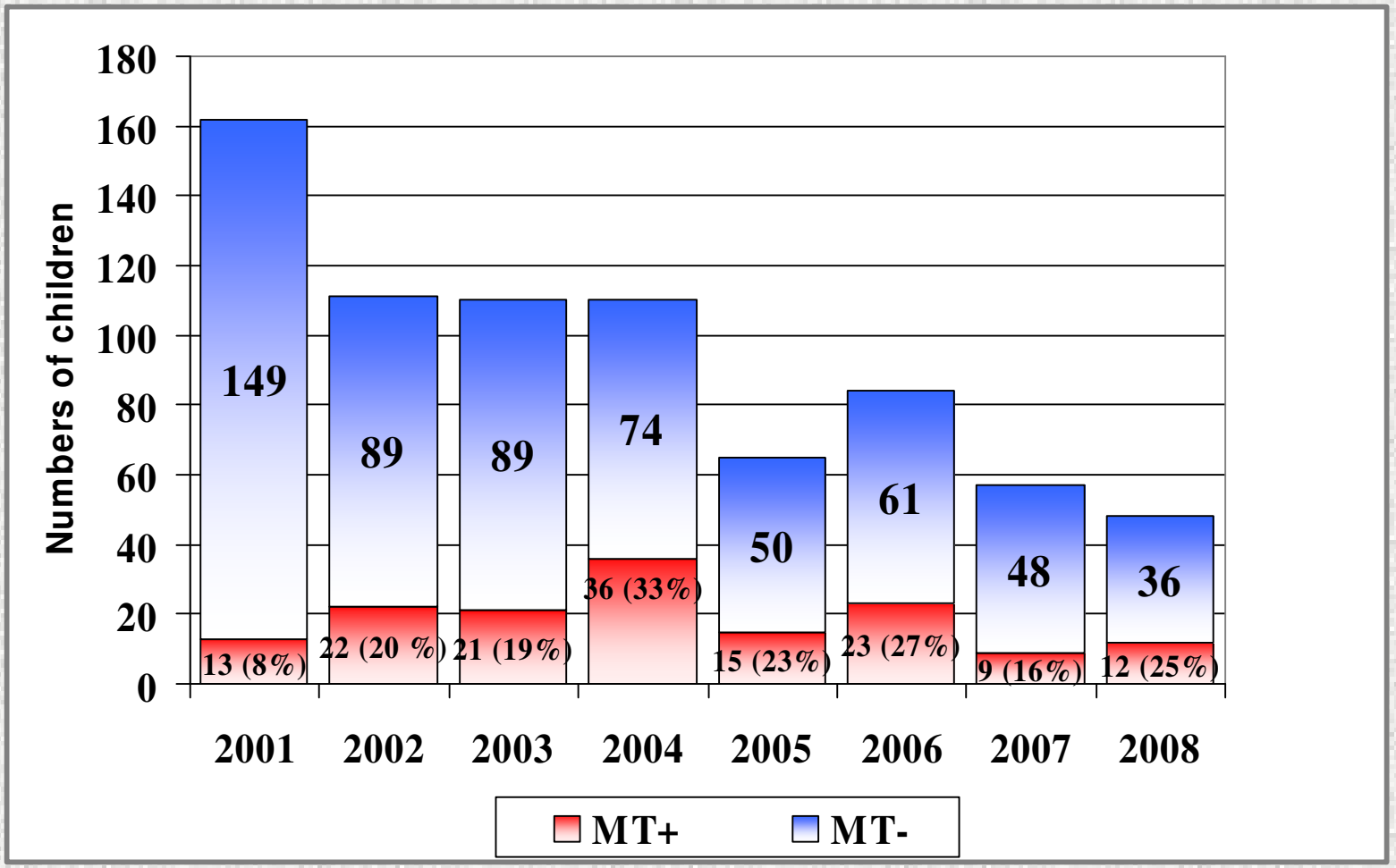
- 9 months old, close contact of mother diagnosed with pulmonary tuberculosis, smear/culture positive for MT, sensitive
- Clinically healthy, BCG vaccinated, *Mantoux* test 15 mm of induration
- Early diagnosis through contact investigation







Bacteriological confirmation of TB in children in Latvia (0-14 years)

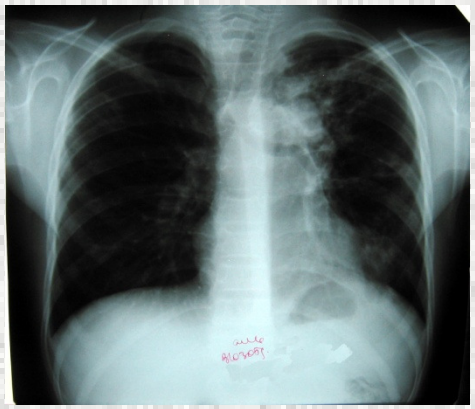


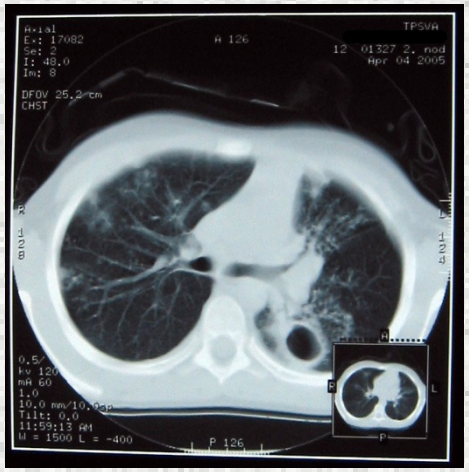
Characteristic features of childhood TB

- Children from 10-15 years about 50% cases develop postprimary adult type disease *(Latvian TB register data)*
- Extensive lung parenchymal involvement and cavities contain large numbers of mycobacteria
- Developing of acquired drug-resistance is available with non-appropriate treatment regimen

Should all children receive the same treatment regimen?

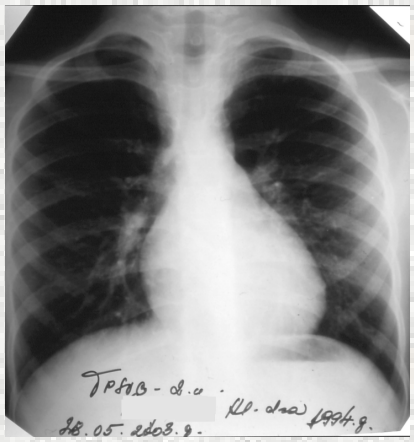
1

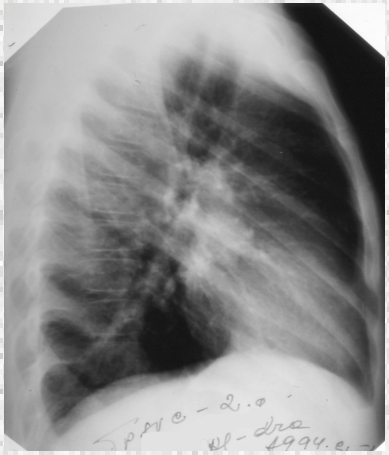




12 years old, sputum sm/cult pos.,drug sensitive, symptomatic

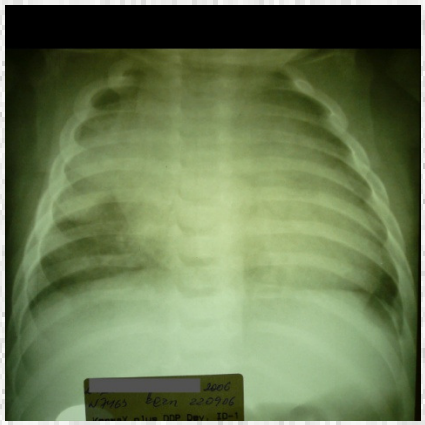
2

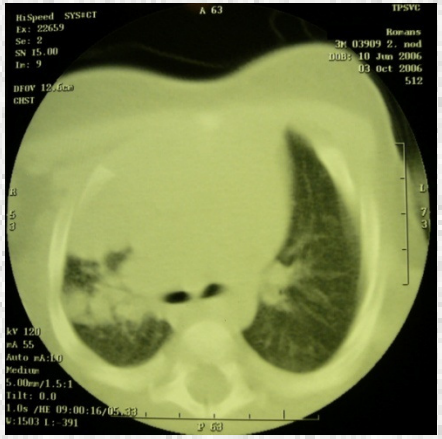




9 years old, sputum sm/cult negative, asymptomatic, infectious source case drug sensitive

3





4 moths old, cult. pos. from gastric asp., drug sensitive symptomatic

Treatment of TB in children

How many drugs?

Which drugs?

Duration of treatment?

Recommended treatment regimens for children in each TB diagnostic category

Category	TB cases	Regimen	
		Intensive phase	Continuation phase
III	1. New smear-negative pulmonary TB (other than in category I) 2. Less severe forms of extrapulmonary TB	2 HRZ	4 HR or 6 HE
I	1.New smear-positive pulmonary TB 2.New smear-negative pulmonary TB with extensive parenchymal involvement 3.Severe forms of extrapulmonary TB (other than TB meningitis) 4. Severe concomitant HIV disease	2 HRZE	4 HR or 6 HE
I	TB meningitis	2 HRZS	4 HR
II	Previously treated smear-positive pulmonary TB: ▪ relapse ▪ treatment after interruption ▪ treatment failure	2 HRZES / 1 HRZE	5 HRE
IV	Chronic and MDR-TB	Specially designed standardized or individualized regimens	

[WHO (2006) Guidance for national tuberculosis programmes on the management of tuberculosis in children]

Recommended treatment regimens for children in each TB diagnostic category

- The use of **streptomycin** in children is mainly reserved for the first 2 months of treatment of TB meningitis
- **Thioacetazone** is no longer recommended as part of first line-line regimen to treat TB
- Regimens **without rifampicin** during continuation phase may be associated with higher rate of treatment failure and relapse
- The dose of **ethambutol 20 mg/kg/day** (range 15-25 mg/kg/day) is safe in children

Treatment of TB in children

Variables to be considered when selecting therapeutic regimen

- Infectiousness of patient
- Disease severity and anatomic location
- Age of patient
- Route of drug administration
- Penetration of medication into certain anatomic sites
- Drug interactions
- Potential medication toxicities
- Underlying diseases
- HIV co-infection
- Drug resistance patterns of isolates

Treatment of TB in children

1. The initial intensive multidrug phase

- Rapidly killing of the majority of viable organisms
- Prevention of emergence of drug resistance

H > S > R > E > Z

2. Continuation phase

- Sterilization of tuberculosis lesions
- Prevention relapse

R > Z > H > S > E

Treatment of TB in children

The treatment of choice for children is directly observed therapy, short course (DOTS) with izoniazid, rifampicin and pyrazinamide for two months, followed by izoniazid and rifampicin for 4 months by following conditions:

- If the child is known to have fully drug-susceptible TB
- Non-cavitary disease
- Sputum smear negative pulmonary TB
- HIV negative
- Young children with primary TB

[WHO (2006) Guidance for national tuberculosis programmes on the management of tuberculosis in children]

Treatment of TB in children

- **Ethambutol** should be added to the initial regimen:
  - High-burden countries
  - if the child failed to fulfil all conditions to be included in treatment category III
- Medications should be administered daily for the first 2- 4 weeks, then may be continued three-times per week

Treatment of TB in children

Duration of treatment

- Usually treatment course of Z and R containing regimens for uncomplicated drug-susceptible TB 6 months is adequate
- Children with miliary TB and/or TB meningitis should be treated for 9-12 months courses *[MMWR Recomm. Rep.52,RR-11 (2003)]*
- Children with cavitary disease, who are sputum culture positive after two months of adequate treatment, should receive treatment up to 9 months, because they are at high risk of relapse *[MMWR Recomm. Rep.52,RR-11 (2003)]*

Treatment of MDR-TB in children

- No published randomized controlled trials for the treatment of MDR-TB in children
- Unresolved controversies in the treatment of drug-resistant TB:
  - The drug resistance testing for second line drugs is not as standardised as for first-line agents
  - In vitro susceptibility is not so closely correlated with clinical response as it is with more commonly used drugs
  - It is unclear, how many drugs, to which the isolate is susceptible has to be used

Treatment of MDR-TB in children

- MDR-TB is a laboratory diagnosis
- Isolation of MT from child's clinical specimens is not available in most cases
- **Early diagnosis** relies on **recognition of potential drug resistance**, based on the contact history and/or response to treatment

Treatment of MDR-TB in children

When the possibility of drug resistance should be considered in the management of children ?

- known adult source case with MDR-TB
- high prevalence of drug resistant TB in the community in which child resides (without known source case)
- an adult source case is treatment defaulter, treatment failure, retreatment case or chronic case with unknown drug susceptibility pattern
- child does not respond satisfactory or deteriorates on TB treatment, or relapses shortly after treatment completion
- child with pulmonary TB relapses after incomplete or incorrect treatment

(Schaaf et al., 2003; Donald, 2007)

Antituberculosis drugs

Grouping	Drugs
Group 1 First line oral agents	isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z);Rifabutin (Rfb)
Group 2 Injectable agents	kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (S)
Group 3 Fluoroquinolones	moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Ofx)
Group 4 Oral bacteriostatic second-line agents	ethionamide (Eto); prothionamide (Pto); cycloserine (Cs); terizidone (Trd); p-aminosalicylic acid (PAS)
Group 5 Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high dose isoniazid (high- dose H); claritromycin (Clr)

High-dose isoniazid can still be used in the presence of resistance to low concentrations of isoniazid (> 1% of bacilli resistant to 0,2 µg/ml but susceptible to 1 µg/ml of isoniazid)

WHO/HTM/TB/2008.402

Treatment of MDR-TB in children

Evidence regarding MDR-TB in children is derived from reported case-series

1. All the treatment should be daily and directly observed
2. Never add a single drug to a failing regimen
3. First line drugs to which the isolate is still susceptible should be used
4. Use at least four drugs certain to be effective
5. Add bactericidal drugs as far as possible

Treatment of MDR-TB in children

6. A fluoroquinolone and injectable should be used if the isolate is susceptible to these drugs

   Injectable drug should be given for a minimum of 6 months, or for at least 4 months after the patient becomes and remains sputum smear- or culture negative.

7. Thionamides, cycloserine / terizidone and PAS can be added

8. Reserve drugs (clofazamine, claritromycin and amoxicillin/clavulanate) with unproven efficacy may sometimes be necessary to use for treatment of extensively drug-resistant TB cases

Treatment of MDR-TB in children

9. If most drugs have been used by patient add those drugs which have not been used in recent past

9. The number of drugs used in treatment depends on the extent and anatomic location of the disease and potency of the available drug as well

11. The optimal duration of treatment for most forms of drug resistant TB in children is unknown. It depends on the extent of the disease, anatomic location, response to therapy, and the exact drug-susceptibility patterns, but in most cases will be 12 months and more. In case of more advanced disease treatment should be at least 12-18 months after the last positive culture, or a minimum of 18 months in total.

Treatment in cases with mono- and poly-resistant TB

Mono - resistance to isoniazid is known or suspected

- Addition of ethambutol to H, R and Z in the intensive phase
- Ethambutol may be continued in the continuation phase lasting 6-9 months
- For patients with extensive disease adding of fluoroquinolone and prolonging the treatment to a minimum of 9 months should be considered

Treatment in cases with mono- and poly-resistant TB

Mono - resistance to rifampicin

1. Intensive phase- isoniazid, ethambutol, fluoroquinolone and pyrazinamide for at least 2 months

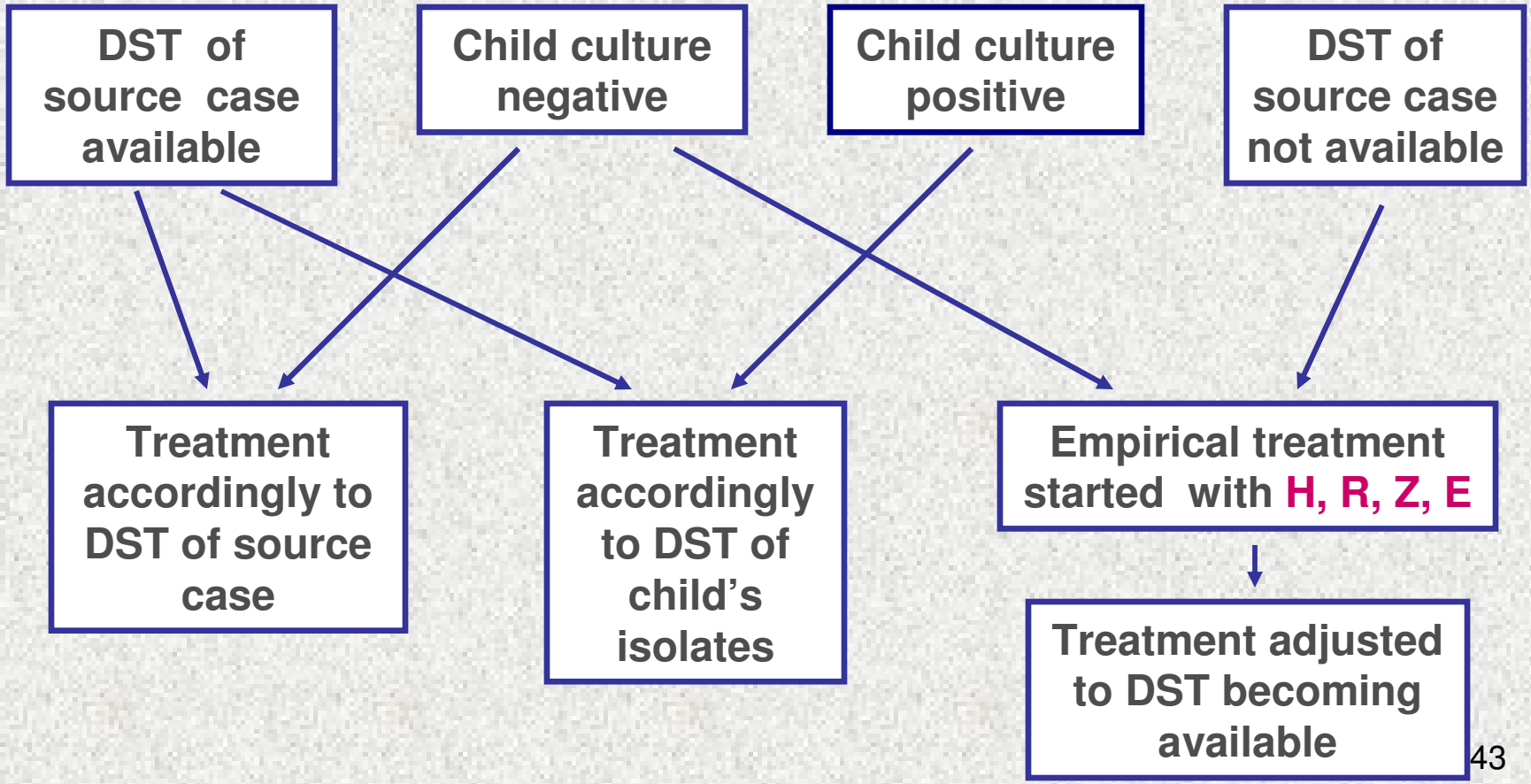
2. Continuation phase – isoniazid, ethambutol and fluoroquinolone for at least 12-18 months

Approach to tuberculosis treatment in children Latvia

- High MDR-TB burden country
- About 70% of paediatric ATB cases are detected through contact investigation
- Bacteriological confirmation and available DST results ranged from 8%-33% during 2001 – 2008 in Latvia
- DOTS strategy, all first- and second- line drugs available

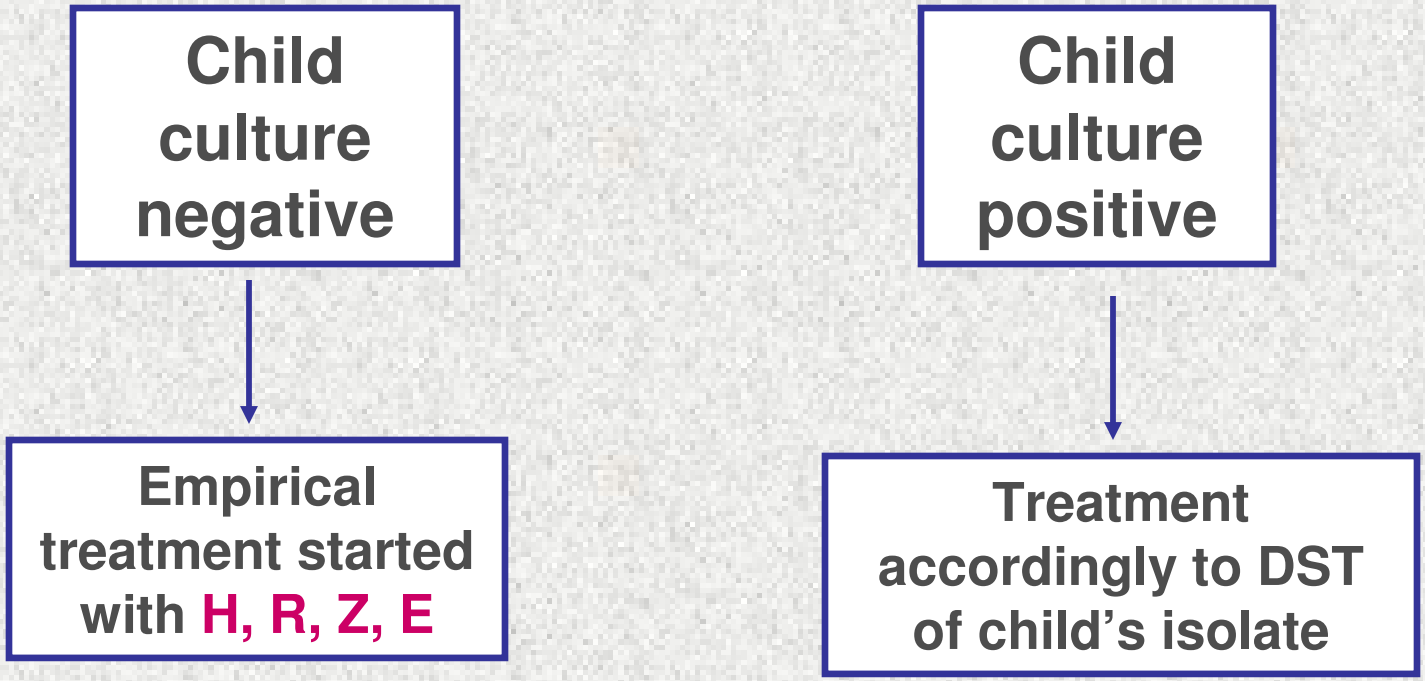
Principles of choice of treatment regimens

Known infectious source case



Principles of choice of treatment regimens (2)

Infectious source case is not known



Summary

- The choice of treatment regimen in child depends on:
  - DST patterns either of infectious source case or child's own isolates
  - Infectiousness, extent and anatomical location of the disease
- For drug-susceptible uncomplicated tuberculosis 6 months multidrug course of izoniazid and rifampicin, supplemented with pyrazinamide for first two months is adeguate
- For infectious, advanced, complicated, doubtfully isoniazid susceptible tuberculosis ethambutol should be added in the intensive phase
- Early diagnosis of MDR-TB relies on recognition of potential drug resistance, based on the contact history. Individualized treatment regimens accordingly to drug susceptibility patterns either of infectious source case of child's own isolates should be used
- All treatment regimens have to be directly observed

Clinical case (1)

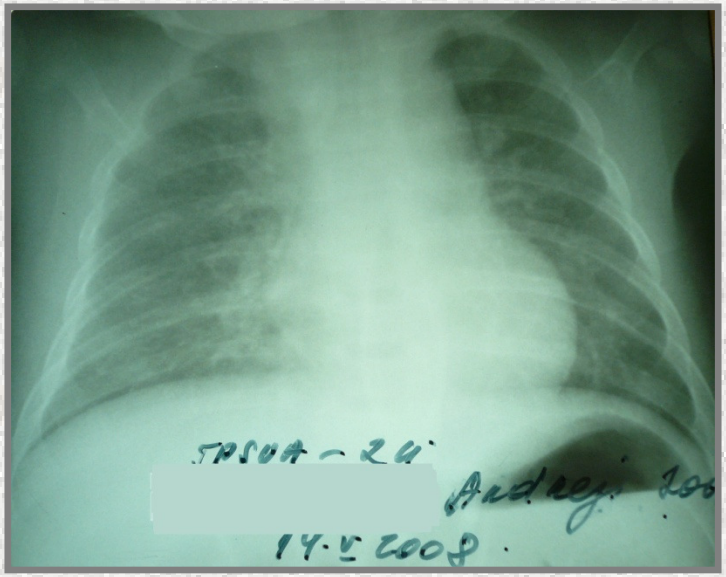
Boy, 5 months old

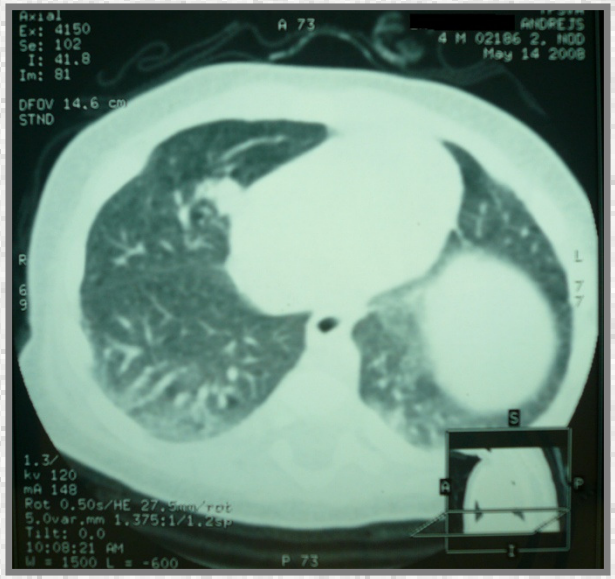
- **Checked for TB, because father was diagnosed with lung tuberculosis, sputum smear positive. Mother was also suspected of having TB, and later diagnosis of lung TB sputum culture positive was confirmed. Source cases *M.tuberculosis* DST data were not yet available on the admission**
- **Preterm child with birth weight 2310 g**
- **Three times wheezing episodes (at ages 1,5 months, 3 months and 1 week before admission)**
- **BCG vaccination has not received**

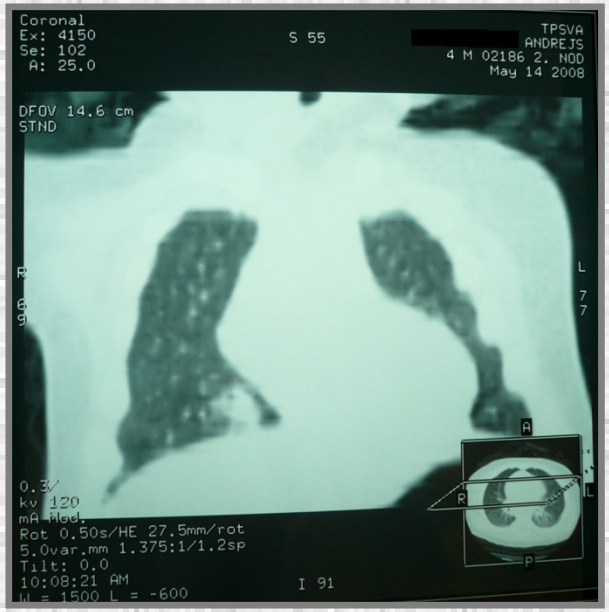
<u>Examination</u>

- **Asymptomatic on the admission on May 13, 2008**
- ***Mantoux* test 16 mm of induration**
- **T SPOT.*TB* test negative**
- **Normal blood count analysis, blood biochemistry and urine analysis**
- **Smear negative from three early morning gastric aspirates**

Diagnosis – primary complex in the middle lobe







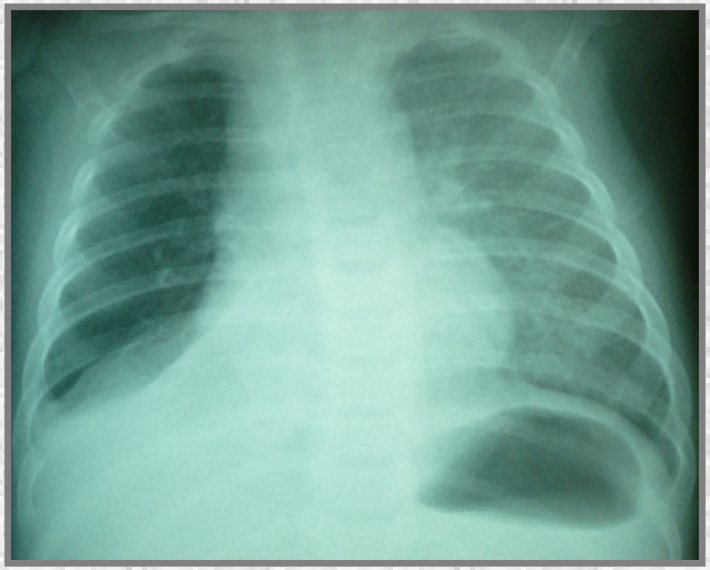
What treatment regimen should be started?

Treatment started with H, R, Z, E on May 15, 2008.

- **DST of father's isolates became available on May 21, 2008. *M.tuberculosis* was sensitive against all first line drugs.**
- **Child's gastric aspirate samples were positive for *M.tuberculosis* on BACTEC medium on June 5, 2008; on solid medium on June 30 (10 col.), and July 1st (2 col.). DST from BACTEC available on June 5, from solid medium on July 21, and showed sensitivity against all first line drugs**

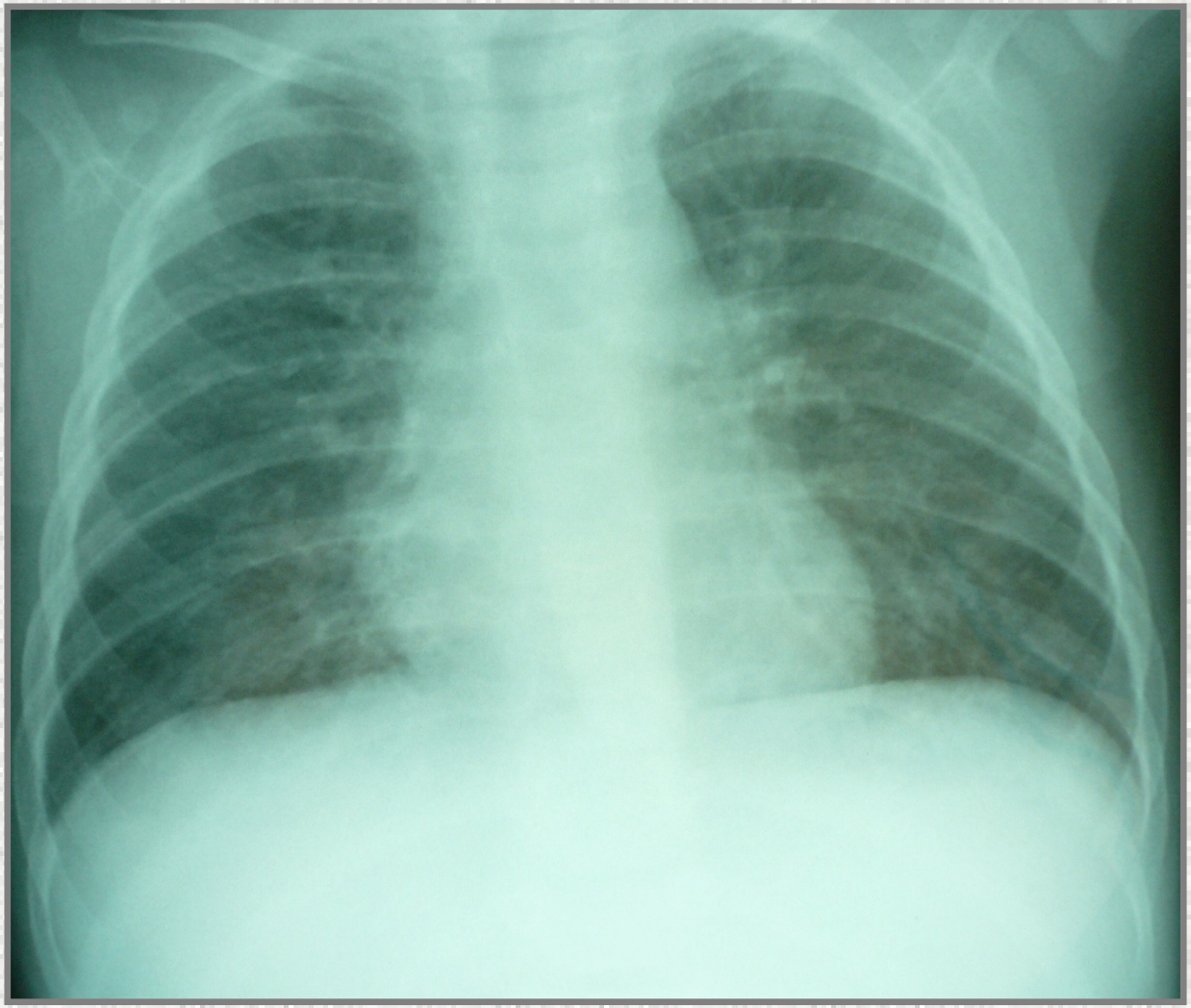
What treatment regimen should be planned?

- Child was treated with H, R, Z, E for 60 days. Chest X-ray improved, and treatment was continued with H and R
- As from beginning of August wheezing and decreased lung sounds on the right lung appeared. On X-ray- atelectasis in the right lower lobe was revealed. On bronchoscopy right main bronchial lumen obstruction with caseous masses was identified. Histology – caseous necrosis and tuberculosis granulation tissue . Weezing disappeared after pathological contents were removed from bronchial lumen



Duration of treatment?

After treatment with 2 H R Z E / 6 H R



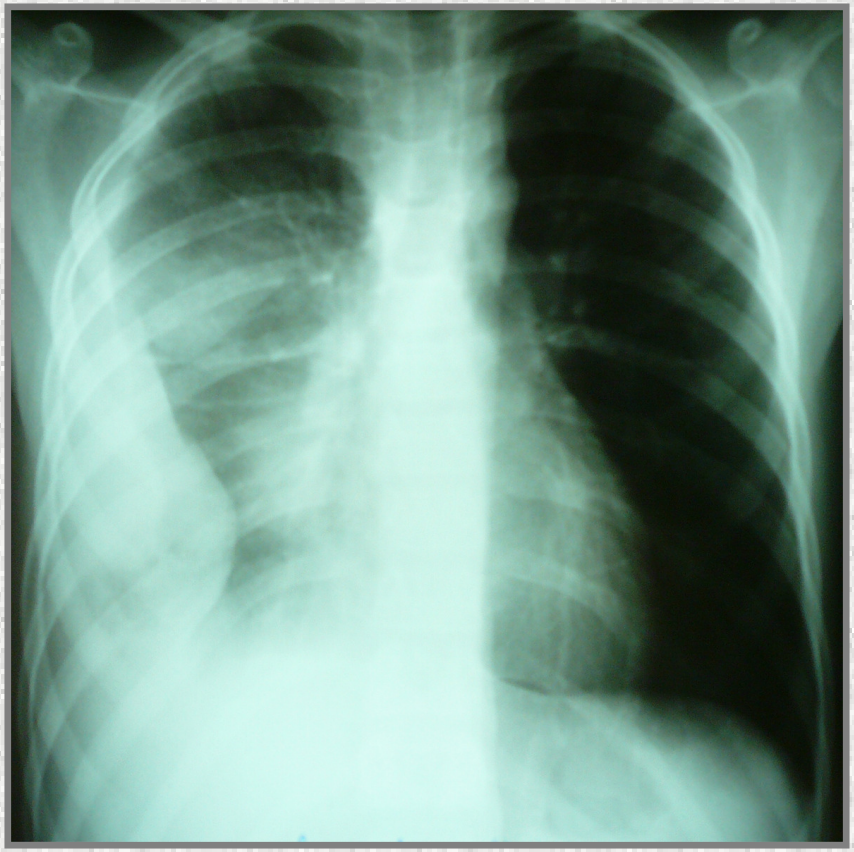
Clinical case (2)

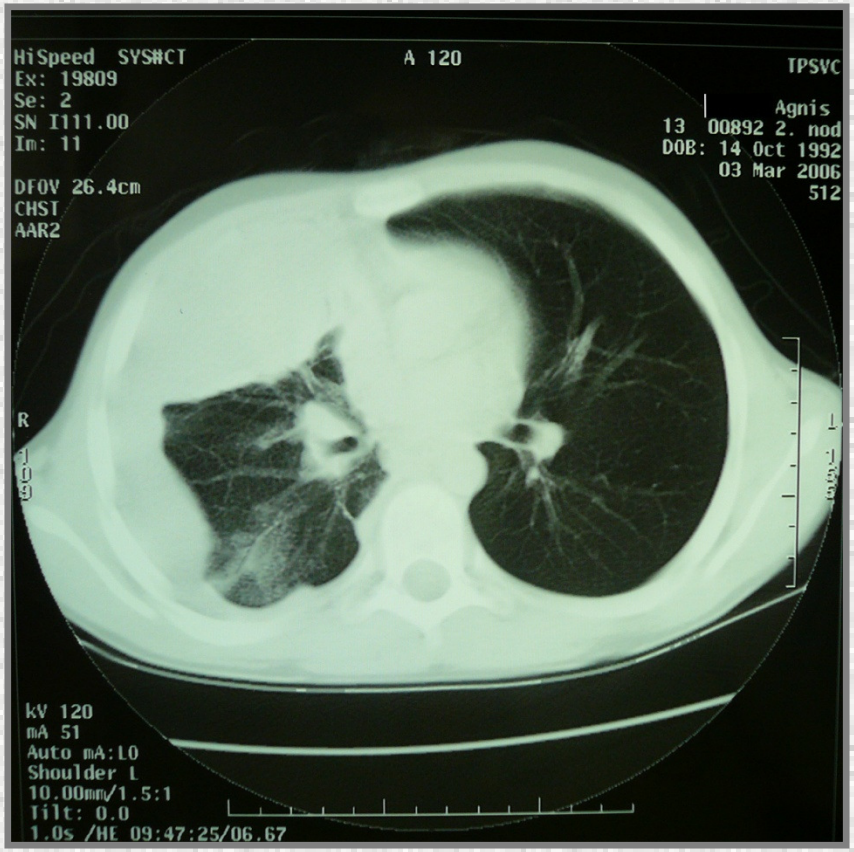
Boy 13 years old

- **Suspected of having tuberculosis pleurisy because clinical and radiological improvement was not achieved after treatment with antibiotics**
- **Clinically symptomatic since February 12, 2006 up to admission in tuberculosis hospital on March 1, 2006**
- **First time mother was diagnosed with lung TB in 2001, sputum smear and culture negative. She had received treatment regimen accordingly to 1st category, but was not fully compliant**
- **After child was suspected of having TB pleurisy, mother was checked and diagnosed with relapse of lung TB, sputum smear and culture positive on March 20, 2006**

Examination

- ***Mantoux*** **test 18 mm of induration**
- **Normal blood count analysis;**
- **CRP 71,31 mg/l;**
- **Pleural fluid analysis - glucose 1,58 mmol/l; LDH 1608 U/l; protein 51,5 g/l; lymphocytes 98%; neuthrophyls 2%.**
- **Histology of pleural biopsy sample - tuberculosis granulation tissue**
- **Smear and later culture negative from 3 induced sputum, bronchial aspirate, pleural fluid and pleural biopsy samples**





<u>Diagnosis</u> – tuberculosis pneumonia and pleurisy

What treatment regimen should be started?

- **Treatment was started with H R Z E on March 2, 2006. Child improved clinically, but radiological improvement was non-significant.**

- **First DST of mother's *M.tuberculosis* were available on May 5, 2006 and showed resistance to H, R, Z, S, sensitivity to E**

Should any corrections in child's regimen be made?

If any, what?

Treatment regimen was changed to Km, Ofx, Pto, E, Trd on May 5, 2006

Further evaluation of mother's DST showed additional resistance to PAS, E, Thioacetazone

Overall mother's MT was resistant to H, R, Z, S, PAS, Thioacetazone; sensitive against Ofx, Km, Cm, Cs, Pto. Discrepant data on E

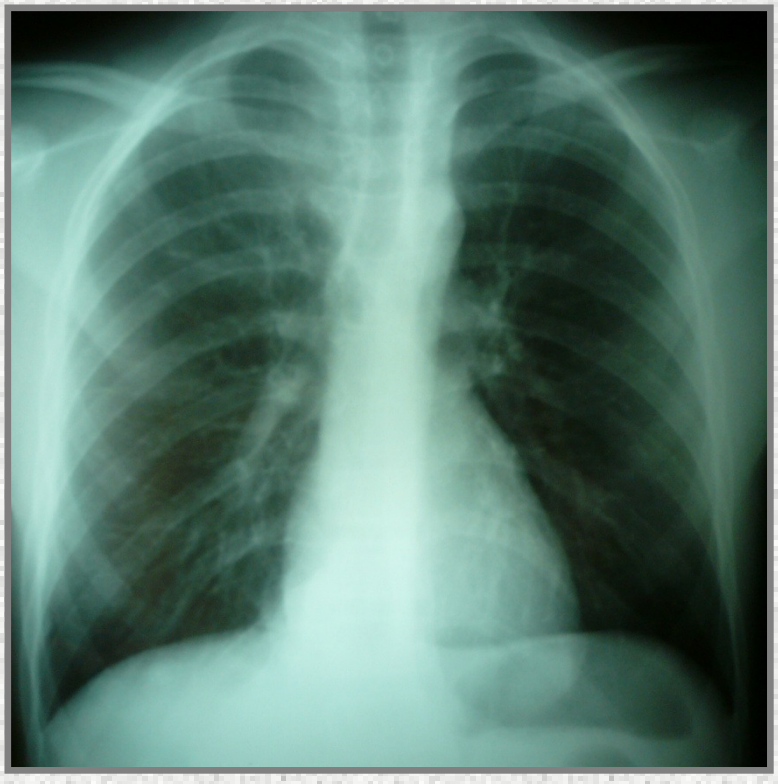
What drugs should be used for child ?

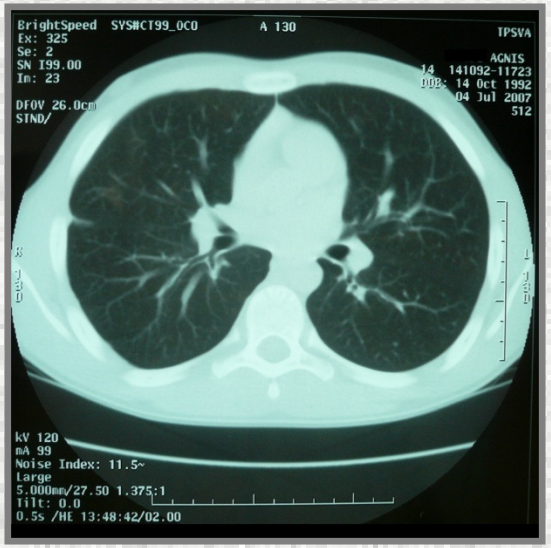
Treatment

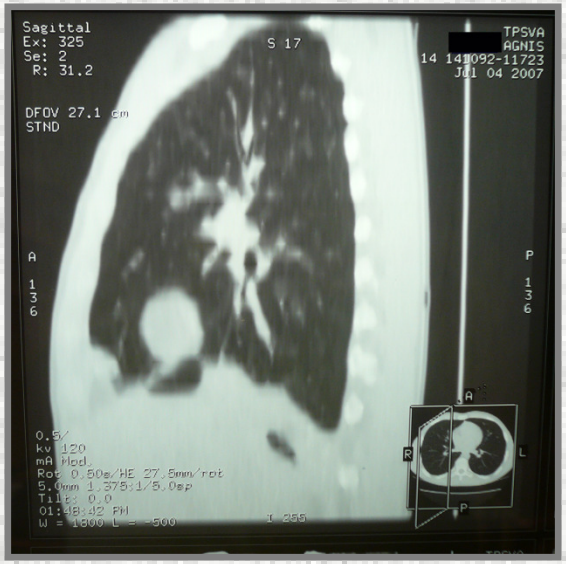
Years and months	2006										2007									
	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10
H	*1*		*5*																	
R	*1*		*5*																	
Z	*1*		*5*																	
E	*1*																			*30*
Km			*6*			*5×*			*3 ×*			*14*								
Pto			*6*																	*30*
Cs			*6*																	*30*
Ofx			*6*																	*30*

Resistant Sensitive Discrepant

After 18 months of treatment







References (1)

1. American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR Recomm.Rep.*52, RR-11 (2003).

2. Cruz, A. T., Starke, J. R. (2008) Treatment of tuberculosis in children. *Expert reviews*, Vol. 6, No 6, 939-957.

3. Corrigan, D. L., Paton, J.Y. (2007) Tuberculosis in children. *Breathe*, Vol. 3, No 4, 351-362.

4. Donald, P. R., Schaaf, H. S. (2007) Old and new drugs for the treatment of tuberculosis in children. *Pediatric Respiratory Reviews*, Vol. 8, Issue 2, 134-141.

5. Donald, P. R., Maher, D., Qazi, S. (2007) A research agenda to promote the management of childhood tuberculosis within national tuberculosis programmes. *INT J TUBERCL LUNG DIS*, Vol. 11, No 4, 370-380.

6. Drobac, P. C., Mukherjee, J. S., Joseph, J. K. *et al*. (2006) Community-based therapy for children with multidrug-resistant tuberculosis. *Pediatrics,* Vol.117, No 6, 2022-2029.

7. Graham, S. M., Bell, D. J., Nyirongo, S. *et al*. (2006) Low levels of pyrazinamide and ethambutol in children with tuberculosis and impact of age, nutritional status, and human immunodeficiency virus infection. *Antimicrobial Agents and Chemotherapy,* February 2006, Vol. 50, No 2, 407-413.

8. Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2008.402.

9. Guidance for national tuberculosis programmes on the management of tuberculosis in children. WHO/HTM/TB/2006.371; WHO/FCH/CAH/2006.

References (2)

10. Schaaf, H.S., Gie, R.P., Kennedy, M. *et al*. (2002) Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-months follow-up. *Pediatrics*, Vol.109 No 5, 765-771.

11. Schaaf, H. S., Marais, B. J., Whitelaw, A. et al. (2007) Culture-confirmed childhood tuberculosis in Cape Town, South Africa: a review of 596 cases. *BMC Infectious Diseases*, Vol. 7, No 140.

12. Schaaf, H. S., Parkin, D. P., Seifart, H. I. *et al.* (2005) Isoniazid pharmacokinetics in children treated for respiratory tuberculosis. *Arch Dis Child*, Vol. 90, 614-618.

13. Schaaf, H. S., Shean, K., Donald, P. R. (2003) Culture confirmed resistant tuberculosis: diagnostic delay, clinical features, and outcome. *Archives of Disease in Childhood*, Vol. 88, 1106-1111.

14. Schaaf, H.S., Victor, T.C., Engelke, E. *et al*. (2007) Minimal inhibitory concentration of isoniazid in isoniazid-resistant *Mycobacterium tuberculosis* isolates from children. *European Journal of Clinical Microbiology and Infectious Diseases*, published online: 9 February 2007.

15. Starke, J. R. (2001) Childhood tuberculosis: treatment strategies and recent advances. *Pediatric Respiratory Reviews,* Vol. 2, 103-112.

16. Somoskovi, A., Parsons, L. M., Salfinger, M. (2001) The molecular basis of resistance to isoniazid, rifampin, and pyrazinamide in *Mycobacterium tuberculosis. Respir Res,* Vol. 2, 164-168.