Status of Pediatric MDR/XDR TB in the Russian Federation

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Challenges for Russian Pulmonologists

- Increasing TB morbidity and mortality rates in the young
- Late disease detection
- Undiagnosed extrapulmonary tuberculosis
- Multi-drug resistant tuberculosis and low rates of treatment effectiveness
- HIV co-infection
- Tuberculosis in prisons
Tuberculosis morbidity by age group in Russia

Source: F. № 33 FSN
Primary characteristics of newly diagnosed adult TB cases

- Population covered by occupational health exams: 61.3%
- Proportion of patients with bacterial excretion: 44.4%
- Proportion of patients with degraded lung tissue: 47.3%
- Proportion of patients with primary multi-drug resistance: 10.7%

Source: F. № 33 FSN
Number of newly diagnosed patients with MDR-TB in 1999-2011

Source: F. № 33 FSN
Total number of patients with MDR-TB in Russia (1999-2011)

Source: F. № 33 FSN
Proportion of newly diagnosed patients with primary MDR-TB in various RF subjects

- High level of primary MDR
- Low level of primary MDR
- Level of primary MDR is in the range of 95% CI, mean in RF.
- No reliable information about the level of primary MDR
Prevalence of MDR-TB

- High level prevalence of MDR-TB
- Low prevalence of MDR-TB (4q)
- Level of prevalence of MDR-TB is in the range of 95% CI, mean in RF.
- No reliable information about prevalence of MDR-TB
Challenges Facing Pediatric Pulmonologists

- Late diagnosis
- Detection of TB in children in advanced stages of disease
- Undiagnosed extrapulmonary TB
- Inefficient TB prevention measures
- Unsatisfactory vaccine prevention
- High incidence of disease in children from high risk groups
Pediatric TB in Russia in 2011

234,629 children were infected with TB

2,818 children and 968 teenagers were diagnosed with active forms of TB

1,437 children were diagnosed with latent TB

Source: F. № 33 FSN
Incidence Rate of TB in Children

per 100,000 children

Source: F. № 33 FSN
Incidence Rate of TB in Teenagers
per 100,000 teenagers
Current Characteristics of TB in Children

- DR TB is found in more than 50% of cases
- TB in young children is due to complications from the Calmette and Guerin vaccines
- TB in primary school-aged children is often found in the intrathoracic lymphatic glands
- Teenagers often present complicated forms of secondary TB
- Lack of new anti-TB drugs for pediatric TB patients
28 of 167 children discharging bacteria had multi-drug resistance, and 76 of 426 teenagers developed multi-drug resistance in Russia in 2011.

Source: F. № 33 FSN
Characteristics of Pediatric DR TB 
(*n*=160, under 14 years)

- The MAIN GROUP had 65 children with DR TB
- The CONTROL GROUP had 95 children with drug sensitive TB
Risk Factors for Developing DR TB Among Children

Type of contact

- Double contact: 15.3% (Main group), 7.3% (Control group)
- Triple contact: 9.2% (Main group), 2.1% (Control group)
- Death focus: 30.7% (Main group), 11.5% (Control group)

p<0.05
Risk Factors for Developing DR TB Among Children

Methods for disease diagnostics in children

<table>
<thead>
<tr>
<th>Method</th>
<th>Proportion of children, %</th>
<th>Main group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per tuberculin diagnostics</td>
<td>64.2</td>
<td>30.9</td>
<td>18.4</td>
</tr>
<tr>
<td>Per contacts</td>
<td>25.6</td>
<td>10.2</td>
<td>10.2</td>
</tr>
<tr>
<td>Seeking medical care</td>
<td>50.7</td>
<td>50.7</td>
<td>25.6</td>
</tr>
</tbody>
</table>

p<0.05
Risk Factors for Developing DR TB Among Children

Proportion of children who received preventative treatment

<table>
<thead>
<tr>
<th>Full course of chemoprophylaxis</th>
<th>Interrupted course of chemoprophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main group 29.2%</td>
<td>Main group 35.4%</td>
</tr>
<tr>
<td>Control group 31.6%</td>
<td>Control group 15.8%</td>
</tr>
</tbody>
</table>

p < 0.01
Analysis of Spectrum of DR TB in Children

• Generalized resistance to first-line TB drugs, especially to streptomycin (89.2%).
• Frequent (39.3%), resistance to kanamycin.
• Children (38.5%) with DR TB had MDR-TB, and 1.5% were totally resistant to TB drugs.
Clinical Picture of Pediatric MDR TB

• The children from the main group were 1.8 times more likely to have acute-onset disease, while children from the control group were three times as likely to have multiple symptoms at the onset of the disease.

• The children from the main group were 2.2 times more likely to have significant symptoms than children from the control group.

• Most frequently, children from the main group were admitted in moderate or severe condition, complaining of chest pains 2.2 times more often, and coughing with virulent sputum 1.6 times more often, due to the progression of the underlying disease and the overlay of increasing secondary resistance.
Drug Sensitivity in Children in the Main Group

- Mono-resistance: 38.5%
- Poly-resistance: 52.3%
- MDR: 9.2%
Course of Treatment Depending on Drug Resistance

• Accelerated disease was typical for children which DR strains (83.9%). Accelerated disease was less often observed in children in the main group (23.9%).

• Latent TB (38.4%) and TB with periods of stabilization and aggravation (20.6%) were observed significantly more often in children in the main group. They were resistant to more than 3 drugs and to first and second line drugs.

• Progressive treatment was recorded only in children with MDR-TB or TDR-TB (17.4%).
MDR-TB Without Chronic Forms of Tuberculosis

- **Mono-resistance**
- **MDR TB in combination with chronic forms of tuberculosis**

### Graph Details

- **Y-axis**: Number of children, n
- **X-axis**: Treatment period, months

#### Legend
- **Main group**
- **Control group**
Dynamics of Morbidity in Children from Contact with Active TB Cases

per 100,000 (contacts)

Source: F. № 33 FSN
Frequency of Contact with the Active TB Case

- Constant: 38%
- Periodic: 62%
Duration of Contact with Active TB Case

- up to the year: 33%
- 2-3 years: 46%
- more than 5 years: 21%
- death focus: 44%
Type of DR TB in Children and Adolescents

- Mono-resistant: 58%
- Polyresistant: 27%
- MDR: 15%
Analysis of the Spectrum of DR TB in Children and Adolescents
Comparative Characteristics of DR TB in Children with Active TB Case

- 24% MDR in infection source
- 28% MDR in children and adolescents
<table>
<thead>
<tr>
<th></th>
<th>Spectrum of MDR-TB in Active TB Case</th>
<th>Spectrum of MDR-TB in children and adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>isoniazide 83,3%</td>
<td>isoniazide 81,2%</td>
</tr>
<tr>
<td>rifampicicine</td>
<td>56,2%</td>
<td>rifampicicine 66,6%</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>2,0%</td>
<td>pyrazinamide 10,4%</td>
</tr>
<tr>
<td>streptomycin</td>
<td>70,8%</td>
<td>streptomycin 81,2%</td>
</tr>
<tr>
<td>ethambutol</td>
<td>18,7%</td>
<td>ethambutol 20,8%</td>
</tr>
<tr>
<td>kanamycine</td>
<td>18,7%</td>
<td>kanamycine 31,2%</td>
</tr>
<tr>
<td>prothionamide</td>
<td>6,2%</td>
<td>prothionamide 31,2%</td>
</tr>
<tr>
<td>PAS</td>
<td>6,2%</td>
<td>PAS 12,5%</td>
</tr>
<tr>
<td>capreomycin</td>
<td>2,0%</td>
<td>capreomycin 14,5%</td>
</tr>
<tr>
<td>cycloserine</td>
<td>-</td>
<td>cycloserine 10,4%</td>
</tr>
<tr>
<td>fluorquinolones</td>
<td>-</td>
<td>fluorquinolones 4,1%</td>
</tr>
<tr>
<td>mycobutin</td>
<td>-</td>
<td>mycobutin 4,1%</td>
</tr>
</tbody>
</table>
Percentage of Infected Children Receiving Preventative Care before Onset of Disease

- 29.70% CP is made
- 70.30% CP is not made
Preventing TB Infection from a Primary Contact

• Timely detection of adult patients.
• Control treatment of patients with chronic forms of tuberculosis.
• Provide reliable isolation of children from persons with bacterial excretion.
• Observe continuity between adult and pediatric district TB services.
• Develop methodical recommendations for methods of preventive treatment of people in contact with DR TB patients.
Challenges

• High morbidity rates among children and adolescents due to contact with TB patients require solving current problems with household infection

• Parents’ refusal of examination and preventative treatment, and a lack of child isolation from the TB patient

• TB patients’ refusal of hospitalization and treatment, especially among patients with chronic disease
Conclusions

• Advanced tissue decay was observed in children and adolescents with pulmonary TB.
• 37.5% had massive bacterial excretion.
• Adolescents were more significantly affected than were children, similar to that of adults.
• Children which have contact with patients with MDR-TB should take preventive therapy with 2 anti-TB drugs for 6 months, which is compulsorily in pediatric sanatoria.
Conclusions

• The presence of MDR-TB in children and adolescents with newly diagnosed tuberculosis may be explained by drug-resistant TB strains (i.e., person-to-person contact).

• The increase of MDR-TB may reflect not only increased morbidity of drug-resistant strains, but also increased performance of dispensaries, laboratory services, on the one hand, and may represent the results of ineffective treatment and insufficiently effective measures of infection control on the other hand.
Methods of Solving the Problem

- Improvement of social-economic situation
- Improvement of drug provision, implementation of modern treatment methods, further implementation of controlled treatment, measures for preventative treatment and premature discontinuation of treatment
- Intensification of surgical care for patients with MDR-TB
- Epidemiological methods: stop contacts with the population by establishing departments for patients with MDR-TB, hospices, and the addition of new beds for nursing care, tuberculosis sanatoria, etc.
Federal Target Program

"Prevention and control of socially significant diseases (2007-2020)"

Subprogram

"Urgent measures to fight tuberculosis in Russia"

Russian Federation

Government Decree

dated November 13, 2001 No 790.
Results of TB treatment have risen considerably following the commencement of the FEDERAL TARGETED PROGRAMME and the national project “Tuberculosis”.

Results of full provision of anti-TB drugs from reserve series of RF subjects were:

- Abacillirovanie MDR contingents from 5.7% to 18.1%
- Abacillirovanie contingents from 30.8% to 41.6%
- Clinical cure rate –28.5% to 34.3%

Source: F. № 33 FSN
Contemporary Diagnostics: in vivo: Diaskintest, in vitro: QuantiFERON and T-SPOT

Evaluation of induration and redness

Skin test

Presentation of mycobacterial antigens

Antigen-representative cell

T-memory cell

Blood test in vitro

Detection of IFN-γ level

TNF-α, IFN-γ, IL-8, etc

TNF-α, IFN-γ, IL-8, etc
DIAGNOSTICS OF TUBERCULOUS INFECTION WITH THE HELP OF RECOMBINANT PROTEINS in vivo
M.tuberculosis Diaskintest®

Technique of skin test with preparation "Diaskintest" is similar to Mantoux test.

Implementator: RUSSIA, I.M. SECHENOV RESEARCH INSTITUTE OF MOLECULAR MEDICINE, MOSCOW MEDICAL ACADEMY
Manufacturer: RUSSIA, PHARMACEUTICAL COMPANY "LEKKO"
REGULATORY BASIS FOR THE USE OF SKIN TEST DIASKINTEST®

ORDER OF RF MINISTRY OF HEALTHCARE AND SOCIAL DEVELOPMENT

No 855 dated October 29, 2009.
"On the introduction of amendments to Annex No 4 to the Order of Ministry of Healthcare of the Russian Federation dated March 21, 2003 No 109":

Complement the Annex No 4 "Directions for Use of Tuberculin Test" with Annex No 2
“Every day TB kills 200 children. And this is despite the fact that the therapy which prevents disease in children is less than 3 cents a day, and treatment of the disease costs 50 cents a day, but before we can provide prevention and treatment, we have to find those at risk of TB, and this is possible only when governments, civil society and the private sector work together.”

Executive Secretary of the Partnership's "Stop TB" Dr. Lucica Ditiu.
Thank you for your attention!